RANDOMIZED DOUBLE BLIND STUDY COMPARING ONDANSETRON, PALONOSETRON & GRANISETRON TO PREVENT POST OPERATIVE NAUSEA & VOMITING AFTER LAPAROSCOPIC SURGERIES UNDER GENERAL ANAESTHESIA

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ABSTRACT: The aim of the study is to compare the efficacy of intravenously administered 5-HT_3 receptor antagonists namely Ondansetron, Palonosetron and Granisetron given as prophylaxis for postoperative nausea and vomiting in patients undergoing laparoscopic surgeries under general anaesthesia. A single dose of palonosetron (0.75 µg) when given prophylactically results in a significantly lower incidence of PONV after laparoscopic surgeries than ondansetron (4mg) and granisetron (2.5mg) during the first 24 hours.

KEYWORDS: Laparoscopic surgery, Ondansetron, Palonosetron, Granisetron, PONV.

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INTRODUCTION: Postoperative nausea and vomiting (PONV) are distressing and frequent adverse events of anaesthesia and surgery, with a relatively high incidence after laparoscopic surgeries.(1) The overall incidence of PONV in recent large studies after general anaesthesia was found out to be approximately between 20% to 30% which is consistently lower than the 75%-80% incidence reported during the "ether era".(2) With the change in the emphasis from an inpatient to outpatient, hospital and office based medical/surgical enhancement, there has been increased interest in the 'big little problem'(3) of PONV.

OBJECTIVES:

1. To determine the efficacy of prophylactic Ondansetron, Palonosetron and Granisetron on the incidence of postoperative nausea and vomiting in adults undergoing elective laparoscopic surgeries under general anaesthesia.
2. To assess the requirement of rescue anti emetic in postoperative period.

MATERIAL & METHODS: The study was conducted in Government Medical College Nizamabad, in the department of anesthesiology.

Study Population: One hundred and forty seven adult patients of either sex slated to undergo various elective laparoscopic surgeries under general anaesthesia belonging to ASA Grade I and II physical status were included in the study. Patients belonged to urban, sub urban and rural population.

Sample Size & Sample Technique: Sample size was calculated on the basis of the primary outcome measure. A Sample size of hundred and forty seven was arrived by using a simplified risk score given by Apfel CC et al for predicting post operative nausea and vomiting in adults.

In the scoring system the risk percentage of post operative nausea and vomiting for patients with one, two, three or four risk factors was found out to be 10, 20, 40, 60 and 80 respectively. Including only patients with at least three risk factors in this study will result in an average control event rate (CER) of approximately 60% and we expected with our antiemetic approach a relative risk reduction of post operative nausea and vomiting of 50%. The absolute risk reduction (ARD- Absolute risk reduction=Baseline risk X Relative risk reduction i.e. 60 X 0.5= 30%), would therefore be 30% and expecting a treatment event rate of 30%. With an α=0.05 and β=0.2 the sample size per group for two proportions (two-sided study) was calculated using statistical software nQuery Advisor 4.0 and a sample size of forty nine per group was arrived i.e. sample size of forty nine in each group has a 80% power to detect a relative risk reduction of 1.54 from the baseline risk with a significance level (alpha) of 0.05 (two-tailed).

Patients were randomly allocated into three groups of forty nine each using computer generated randomization technique and received the following medication intravenously two minutes prior to induction of anaesthesia.

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Group – A	49 Patients	Ondansetron	4 mg
Group – B	49 Patients	Palonosetron	0.75 µg
Group – C	49 Patients	Granisetron	2.5 mg

Table 1

Study Design: Prospective randomized double blind study.

Data Collection Technique and Tools: Detailed history was taken from the patient. Clinical examination and pre anesthetic assessment was done. Demographic data was noted. Standard anaesthetic technique was used and vitals parameters were monitored intraoperatively. The incidences of post operative nausea and vomiting (nausea, retching and vomiting) were recorded with in the first 24 hours after surgery at intervals of 0-2hours, 2-3hours and 3-6hours in postanaesthesia care unit and from 12 hours to 24 hours in postoperative ward. Complete response (free from emesis) was defined as no post operative nausea and vomiting (nausea, retching and vomiting) and no need for any rescue antiemetic during the 24-hour observation period. Inj. Metoclopramide 10 mg i.v was used as rescue antiemetic. The adverse effects were also monitored.

Data Analysis: The raw data was entered into a Microsoft Excel spreadsheet and analyzed using Graphpad Instant (Version 3.10), Graphpad Prism 6(version 6.03) and Graphpad Statmat_2 (version 2.00) for Windows Seven.

For descriptive statistics means, standard deviation and percentages were calculated. One way Analysis of variance (one way ANOVA) was used to see the mean differences between the three groups. Fisher's exact test and chi-square test was employed for intergroup comparison of categorical variables. A two-sided p value of <0.05 was considered statistically significant. vagus nerve afferent fibers.

OBSERVATION AND RESULTS: The incidence of PONV after laparoscopic surgery is high (40-75%). The etiology of PONV after laparoscopic surgery is complex and is dependent on a variety of factors including age, obesity, and history of previous PONV, surgical procedure, anesthetic technique and post-operative pain.

In this study, however, all the groups were comparable with respect to patient demographics, anaesthetic technique and analgesics used postoperatively. No significant differences in baseline demographic or clinical characteristics were found between the study groups. Therefore the difference in a complete response (no PONV, no rescue medication) between the groups can be attributed to the study drug. The anaesthetic technique was standardized (general anaesthesia with controlled ventilation) in all patients.

In our study, the dosage selection of ondansetron (4mg) was based on the previous studies done by Naguib M [(4)] et al in 1996 Argiriadou H [(5)] et al in 2002 and Elhakim M et al in 2002.[(6)] The dose of granisetron 2.5 mg (approximately 45µg kg^{-1}) selected for this study was within its effective dose range (40-80µg kg^{-1}) was based on the study done by Mikawa K et al in 1995 and Fujii Y et al in 2004 and 2006. However, the dose of palonosetron to be used for the prevention of PONV is not established but was extrapolated from the dose used in the clinical trials. Candiotti KA and colleagues demonstrated that palonosetron 75µg is the more effective dose for the prevention of PONV after major gynecological and laparoscopic surgery than 25µg and 50µg.

It was decided to administer the study drug two minutes before the induction of anaesthesia on the basis of previous studies by Honkavaara P in 1996, Biswas BN et al in 2003 and Bhattacharya D and Banerjee A in 2003.

In the present study we compared the antiemetic efficiency of ondansetron, palonosetron and granisetron post operatively for laparoscopic surgeries for first 24 hours.

Drug	Nausea	Retching	Vomiting
Ondansetron	18(36%)	9(18%)	14(28%)
Palonosetron	4(8%)	1(2%)	3(6%)
Granisetron	7(14%)	5(10%)	10(20%)

Table 2

In ondansetron group 18 patients (36%) complained of nausea, 9 patients (18%) complained of retching and 14 patients (28%) had vomiting episodes, 4 patients (8%) complained of nausea 1 patient (2%) complained of retching, 3 patients (6%) had vomiting episodes in palonosetron group and in granisetron group 7 patients (14%) complained of nausea, 5 patients (10%) complained of retching and 10 patients (20%) had vomiting episodes. Incidence of nausea, retching and vomiting episodes were high in ondansetron group than in palonosetron and granisetron group.

The merged total early incidence of post operative nausea and vomiting (PONV) i.e. in the first 12 hours for patients in ondansetron group was higher when compared to palonosetron group and was statistically significant (P value is 0.0453; Relative risk = 4.000; 95%Confidence Interval: 0.8939 to 17.898). Merged total early incidence of post operative nausea and vomiting (PONV) i.e. in the first 12 hours for patients in granisetron group was higher when compared to palonosetron group and statistically significant (P value is 0.0453; Relative risk = 0.2500; 95% Confidence Interval: 0.05587 to 1.119) whereas comparison between ondansetron and granisetron (P value is 1.0000; Relative risk = 1.000; 95% Confidence Interval: 0.4079 to 2.451) was statistically not significant.

The merged total net incidence of PONV (nausea, retching and vomiting) after 24 hours was 34% in the ondansetron group, which was higher than in palonosetron group and granisetron group which had 6% and 20% incidence respectively.

	P Value	Relative risk	95% confidence interval
Ondansetron v/s Granisetron	0.1135	1.700	3.334
Ondansetron v/s Palonosetron	0.0008	5.667	1.773 to 18.113
Granisetron v/s Palonosetron	0.371	0.300	0.0371
Comparison of efficacy between three groups			

Palonosetron was more effective in preventing PONV than ondansetron and granisetron this difference was highly statistically significant (P value = 0.0008; Relative risk = 5.667; 95% Confidence Interval: 1.773 to 18.113 for ondansetron vs. palonosetron, and P value = 0.0371, Relative risk = 0.300; 95% Confidence Interval: 0.0371 granisetron group vs. palonosetron). Comparison of efficacy between ondansetron and granisetron group (P value = 0.1135; Relative risk = 1.700; 95% Confidence Interval: 0.8669 to 3.334) was not statistically significant.

Out of the total 17 patients in group A who had PONV 6 patients needed rescue antiemetic once and 3 patients were given rescue antiemetic twice as compared to granisetron group in which 2 patients out 10 were given twice whereas rescue antiemetic was given to only one patient in palonosetron group.

Dipasri Bhattacharya[7] compared ondansetron and granisetron for prevention of nausea and vomiting following day care gynaecological laparoscopy reported that granisetron is superior than ondansetron with in first 12 hours post operatively for prevention of PONV, these results are comparable to our study.

Bhattacharjee DP[8] did a comparative study between palonosetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy. In this study it was found that prophylactic therapy with palonosetron is more effective than granisetron which is in agreement with our study.

Wu S-J, Xiong[9] did a systematic review and meta-analysis for comparison of the efficacy of ondansetron and granisetron to prevent PONV after laparoscopic cholecystectomy and concluded that the ondansetron is equivalent to granisetron for preventing early and total incidence of PONV after laparoscopic cholecystectomy. The findings in this study were similar to our study.

Basu A,[10] compared palonosetron, granisetron and ondansetron for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery in this study it was found that a single dose of palonosetron is a superior anti-emetic to granisetron and ondansetron in complete prevention of postoperative nausea and vomiting after middle ear surgery during the first 24 hours period. These findings are in concordance with our study.

Complete response (free from emesis) was defined as no PONV (nausea, retching and vomiting) and no need for any rescue antiemetic during the 24-hour observation period post operatively was noted. In the present study complete response occurred in 66% of the cases in the ondansetron group which is comparable to the studies conducted by Naguib M [4] et al in 1996 and Biswas BN[11] et al in 2003. Complete response in palonosetron occurred in 94% of the cases which is in comparison to work done by Basu A,[10] Bhattacharjee DP.[8] The complete response in the granisetron group occurred in 80% which is comparable to work done by Bhattacharjee DP.[8]

With regard to adverse effects the three drugs were relatively well tolerated. In Group A four patients and one patient each in Group B and C complained of headache. One patient had dizziness in Group A while no patients in Group B and C had dizziness. Rashes and allergic reactions were not reported in the entire study population. All events were of mild to moderate severity and settled spontaneously without separate treatment. It was not possible to link these adverse events conclusively to the prophylactic antiemetic medication received (i.e. to ondansetron, palonosetron and granisetron) as all patients were also receiving prophylactic antibiotics and analgesic medication (diclofenac), in addition to the drugs they had received as pre-anesthetic medication and during anaesthesia.

DISCUSSION: Nausea and vomiting following general anaesthesia has been a distressing problem for the patients and is frequently listed among the most important preoperative concerns apart from pain.[12] With the change in emphasis from inpatient to outpatient office based medical/surgical environment, there has been increasing interest in the "The big little problem"[3] of postoperative nausea and vomiting following general anaesthesia.

In spite of much advancement in the management of postoperative nausea and vomiting with the invention of new drugs, multimodal approaches of management like administering multiple antiemetic medications, less emetogenic anaesthetic techniques, adequate intravenous hydration, adequate pain control etc., the incidence of postoperative nausea and vomiting remains still high, ranging from 25% - 55% following inpatient surgery and 8% - 47% following outpatient surgery.

An effective antiemetic that could be used to treat nausea and vomiting without extending recovery time and that remain effective for 24 hours following treatment would be significant asset to the anaesthesiologist's armamentarium, especially in settings like office based anaesthesia where the patient is admitted for day care surgery and discharged on the same day. Drugs acting for longer duration also have an advantage in surgeries where the incidence of postoperative nausea and vomiting is very high like laparoscopic surgery, middle ear surgery, tonsillectomy, laparotomy, strabismus surgery, orchidopexy etc.

Unfortunately commonly used antiemetic medications like antihistamines, anticholinergics, gastroprokinetics, and butyrophenones cause's undesirable side effects like sedation, dysphoria, restlessness and extrapyramidal

symptoms. To overcome this later serotonin antagonists like Ondansetron, Tropisetron, Dolasetron, Granisetron and Palonosetron were introduced for treatment of nausea and vomiting.[13] They were primarily used in treating chemotherapy induced vomiting with minimal and clinically acceptable side effects. The most distressing and intolerable emesis induced by antimalignant medication was better controlled with these $5HT_3$ antagonists and they proved to have a promising role in the field of oncology. Abundant research in oncology demonstrates the efficacy of these drugs. However there were many reports in the literature about their role in prevention of postoperative nausea and vomiting.

Postoperative period is associated with variable incidence of nausea and vomiting depending on the duration of surgery, the type of anaesthetic agents used (dose, inhalational drugs, and opioids), smoking habit etc. 5-HT_3 receptor stimulation is the primary event in the initiation of vomiting reflex. These receptors are situated on the nerve terminal of the vagus nerve in the periphery and centrally on the chemoreceptor trigger zone (CTZ) of the area postrema. Anaesthetic agents initiate the vomiting reflex by stimulating the central 5-HT_3 receptors on the CTZ and also by releasing serotonin from the enterochromaffin cells of the small intestine and subsequent stimulation of 5-HT_3 receptors on.

CONCLUSION: PONV is one of the most distressing side effects of anaesthesia and surgery with a high incidence following general anaesthesia. Post-operative nausea and vomiting is a highly integrated and complex phenomenon and multi-factorial in origin. The different contribution from each factor depends upon the precise clinical situation. The incidence of PONV after laparoscopic surgery is high (40-75%) and is dependent on a variety of factors including age, obesity, history of previous PONV, surgical procedure, anesthetic technique and post operative pain. PONV may delay patient discharge from post anaesthesia care units (PACUs) and can be the leading cause of unexpected hospital admission after ambulatory anaesthesia.

The quest for more effective anti emetic drugs without the potential for sedative or extrapyramidal side effects has led to the development of a relatively a new class of drugs, 5HT3 antagonists of which ondansetron was the prototype. The need for drugs with improved performance within this group arose on account of relatively less potency and shorter duration of action, besides detectable binding to other $5HT_3$ receptors by ondansetron. Granisetron is a potent and highly selective $5HT_3$ receptor antagonist that has little or no affinity for other $5HT_3$ receptors. Palonosetron is a novel 5-HT_3 receptor antagonist with a greater binding affinity for this receptor and little or no affinity for other receptors and longer biological half-life than older 5-HT_3 receptor antagonist.

Palonosetron was more effective in preventing PONV than ondansetron and granisetron this difference was highly statistically significant (P value = 0.0008; Relative risk = 5.667; 95% Confidence Interval: 1.773 to 18.113 for ondansetron vs. palonosetron, and P value = 0.0371, Relative risk = 0.300; 95% Confidence Interval: 0.0371 granisetron group vs. palonosetron). Comparison of efficacy between ondansetron and granisetron group (P value = 0.1135; Relative risk = 1.700; 95% Confidence Interval: 0.8669 to 3.334) was not statistically significant.
In conclusion from this study it has been found that a single dose of palonosetron (0.75 µg) when given prophylactically resulted in a significantly lower incidence of PONV after laparoscopic surgeries than ondansetron (4mg) and granisetron (2.5mg) during the first 24 hours.

LIMITATIONS OF THE STUDY:

1. We did not include a control group receiving placebo in our study. Aspinall and Goodman [14] have suggested that if active drugs are available, placebo controlled trials may be unethical because PONV are very much distressing after laparoscopic surgery.
2. The patients with underlying diseases were excluded, so the results of the study should not be generalized to other patients with severe underlying diseases.
3. We did not address the issues of economy and surrogate variables like hospital discharge times, expenses incurred towards treating established post operative nausea and vomiting and sequelae of post-operative nausea and vomiting.

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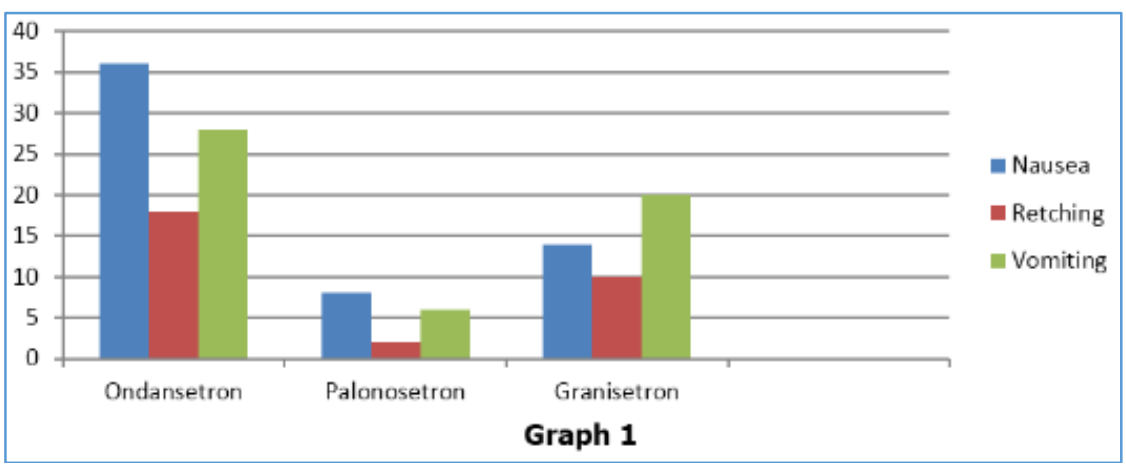

Graph 1