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A comparison of palonosetron and aprepitant for prevention of post operative nausea and vomiting in females undergoing laparoscopic hysterectomy under general anesthesia

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***Abstract*---**Background: Postoperative nausea and vomiting (PONV) is the second most common complaint following pain after surgery. In this era of daycare and outpatient-based surgery, PONV is the cause of delayed recovery and discharge from hospital settings. This study was designed to compare Palonosetron and Aprepitant for the prevention of PONV in patients undergoing laparoscopic hysterectomy under general anesthesia. Methods: 70 patients were included in this randomized double-blind study. Each group was allocated to receive either 0.075 mg of intravenous Palonosetron or 40mg of oral Aprepitant for PONV prophylaxis. A standard regimen of general anesthesia was administered to both groups for surgery. The primary outcome was the PONV impact severity scale (PISS) score at 48 hours following surgery in both groups. Secondary outcomes were the

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incidence of clinically significant PONV in both groups and the requirement of rescue antiemetics. Results: Mean PISS score at 48 hours was significantly lower (0.91±0.13 vs 3.43±0.2) in the Palonosetron group than in the Aprepitant Group. Incidence of PONV (16/35 vs 33/35) was significantly lower with Palonosetron. Incidence of clinically significant PONV and requirement of rescue antiemetics was significantly lower (2/35 vs 13/35) in the Palonosetron group. More patients achieved complete treatment of PONV at 48 hours with Palonosetron than with Aprepitant (19/35 vs 2/35). Conclusion: Palonosetron was superior to Aprepitant in preventing PONV for up to 48 hours in patients undergoing laparoscopic hysterectomy under general anesthesia.

***Keywords*---**PONV, palonosetron, aprepitant, laparoscopy, gynecological.

Introduction

Post Operative Nausea and Vomiting (PONV) is a common and distressing complication of anesthesia. It is defined as the occurrence of nausea, retching or vomiting during first 24-48 hours after surgery in in-patients [1]. Its incidence is about about 20-30% of patients in the post operative period [2]. PONV may be triggered by various pathways through peripheral and /or centrally located receptors; however, the exact etiology remains unknown. Factors associated with PONV include patient age, gender, type and duration of surgery, anesthetic factors, smoking, history of motion Sickness, etc. The incidence of PONV in laparoscopic gynecological surgery is approximately 80% [3]. Female gender and increased intra-abdominal pressure during laparoscopic procedures increase the risk of PONV. It is a significant problem in modern day anesthesia practice. With the change in emphasis from an inpatient to outpatient hospital and office based medical/surgical environment, a holistic approach should be attempted before and during surgery to prevent PONV.

5-hydroxytryptamine type 3 (5-HT3) receptor antagonists are the most commonly used for the prevention of PONV because of their efficacy and low side-effect profile. Palonosetron is effective for the prevention of PONV and was approved in 2008 by the US Food and Drug Administration (FDA) for the prevention of PONV for up to 24 hr post-surgery [4]. Aprepitant is a highly selective NK1 receptor antagonist and was the first drug of its class approved by the US FDA [5]. Jae Hwa Yoo Et al [6] conducted a study evaluating the combination of Palonosetron and Aprepitant with Palonosetron alone for the prevention of postoperative nausea and vomiting in female patients using intravenous patient-controlled analgesia, and found there to be no difference between the two groups in the incidence and severity of PONV during the first 24 hours after surgery. Hyoung Yong Moon Et Al [7] in their study comparing Palonosetron and Aprepitant for the prevention of postoperative nausea and vomiting in patients indicated for laparoscopic gynecologic surgery, found both agents to be equally effective.

The meta-analysis conducted by Vania Milnes Et Al [8] concluded that Aprepitant is more effective in decreasing the incidence of PONV postoperatively as compared with ondansetron and recommended that Aprepitant can be used to treat patients at risk for PONV and for whom PONV could lead to catastrophic adverse outcomes. In this study, we aimed to compare the efficacy of Palonosetron to that of Aprepitant for the prevention of PONV in females undergoing Laparoscopic hysterectomy.

Materials and Methods

This was a randomized double blinded study conducted at VSS Institute of Medical sciences and Research, Burla, Odisha. The study population included all females undergoing laparoscopic surgery enrolled between November, 2019 to October, 2021. Based on a previous study [7], a sample size of 62 patients was required to show a 20% difference in Post operative nausea and vomiting impact scale score11 (PISS) at 48 hours post operatively, considering an error margin of 5% and a power of 80%. Considering a dropout rate of 10 %, a total of 70 patients were enrolled in the study. Sample size was calculated using ClinCalc.com (©2018 - ClinCalc LLC.) Institution Ethical committee approval was obtained before proceeding the study and it was registered in clinical trial registry India with CTRI registration number (CTRI/2021/01/030613). Informed written consent was obtained from all the participants. Information about the study type, the drug, its benefits and side effects were clearly explained and willingness of the patient to participate in the study was documented. 70 females aged between 18 to 65 years under ASA grade1 &2 scheduled to undergo laparoscopic surgery were included in the study. Pregnant females, females weighing ≤45kg and ≥100kg, smokers, having history of motion sickness/ PONV, steroid use, abnormal liver function test and abnormal renal function test were excluded from the study. Patients were randomly assigned to one of the two groups, as decided by computer generated randomization schedule. (fig. 1)

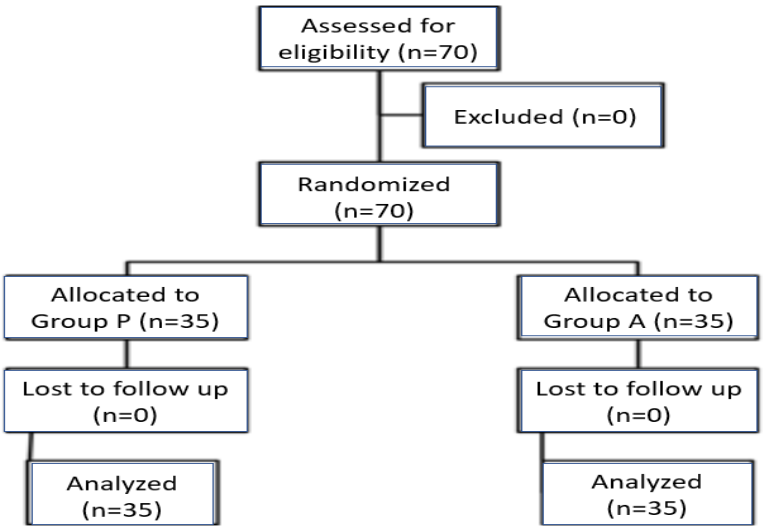

Fig. 1. CONSORT Diagram

The Aprepitant group (group A) was given 40mg of Aprepitant reconstituted with 30ml of water orally, followed by 20ml of water orally 90 minutes before anesthesia induction. The Palonosetron group (Group P) were given equal amount of water, i.e, 30ml followed by 20 ml orally. The palonosetron group (group P) were given 0.075mg of palonosetron i.v immediately after endotracheal intubation whereas the patients in group A received an equal volume of normal saline.

Standard anesthetic regimens were used for all patients. Electrocardiography, non-invasive blood pressure and pulse oximetry were attached after the patient entered the operating room. All the patients in both the groups were given glycopyrrolate 0.004mg/kg i.v , midazolam 0.04mg/kg i.v, nalbuphine 0.2mg/kg i.v as premedication. Anaesthesia was induced with Propofol 2mg/kg and tracheal intubation is facilitated with vecuronium 0.1mg/kg. Anaesthesia was maintained with Oxygen and Nitrous oxide mixture in ratio of 1:2 and sevoflurane titrated according to the depth of anesthesia, along with intermittent doses of vecuronium. End tidal carbon dioxide was monitored in all patients post intubation. Intra-abdominal pressure was maintained between 8-12 mmHg. Heart rate and blood pressure was maintained within 20% of the preoperative values. Neuromuscular blockade was reversed with Injection Neostigmine 0.04mg/kg and Injection Glycopyrrolate 0.004 mg/kg. In the immediate postoperative period patient was shifted to recovery room for monitoring of vitals which includes heart rate, electrocardiogram and oxygen saturation. All the anesthetic procedures were performed by a single anesthesiologist. The participant and outcome assessor were blinded to treatment allocation. The occurrence of nausea and vomiting, the severity of nausea was recorded according to a PONV Impact Scale Score [9].

PONV Impact Scale Score (PISS)

Questions	Answers	Score*
Did you have vomiting or dry retching?	No	0
	Once	1
	Twice	2
	Three or more times	3
Have you experienced a feeling of nausea? If yes, has it interfered with your daily activities?	Not at all	0
	Sometimes	1
	Often/most of the times	2
	All the time	3

*Addition of numerical responses to questions 1 and 2 gives the PONV impact scale score. PONV Impact Scale Score of ≥5 defines clinically important PONV. PONV=Postoperative nausea vomiting

The PISS score was used to quantify the severity of nausea and was recorded up to 48 hours post operatively at 2,6,12,24,48 hours. PISS score≥5 was defined as clinically significant PONV. PONV treatment completion was defined as PISS score of zero for 48 hours after surgery. When a patient experienced a PISS score ≥5, 10 mg of Metoclopramide was administered i.v. When the symptoms did not improve at follow up, 5mg of dexamethasone was administered i.v. Diclofenac and paracetamol was administered for post operative pain, depending on the severity. Adverse effects, if any, were identified and treated.

All data was collected in a pre-described proforma and tabulated using Microsoft® Excel® 2016. Statistical analysis was performed using SPSS (version 22, SPSS Inc, Chicago, IL). Categorical data was compared using the Chi-square test. Parametric data was compared using the independent t-test and non- parametric data was compared using the Mann-Whitney U test. A p value of less than 0.05 was considered statistically significant.

Results

The comparison between demographic data and duration of surgery in both the groups is shown in Table 1. Both the groups were comparable in terms of demographic profile with no statistical significance. Duration of anesthesia was 116.00 ± 15.18 mins in group P and 119.89 ± 19.03 mins in group A with a p value of 0.348, hence not significant statistically.

Table 1. Demographic data and duration of anesthesia

Parameters	Group P (n=35) Mean (SD)	Group A (n=35) Mean (SD)	P Value
Age in years	46.6 (4.3)	48.2 (5.1)	0.058
BMI	22.86 (2.7)	22.95 (2.8)	0.88
Duration of Anesthesia in minutes	116.00 (15.18)	119.89 (19.03)	0.348

The incidence of PONV in patients of both groups in the 48-hour period is listed in Table 2 and shown in Fig. 2. There were no patients with incidence of PONV in the 0-2 hr and 2-6 hr period in Group P. 6 patients, 11 patients and 16 patients respectively in the 6-12 hr, 12-24 hr and 24-48 hr period in Group P were recorded to have PONV. For Group A, the numbers were 8, 14, 23, 30 and 33 respectively for 0-2 hr, 2-6 hr, 6-12 hr, 12-24 hr and 24-48 hr periods. Incidence of PONV was significantly higher at all times in Group A as compared to Group P.

Table 2. Incidence of PONV in post operative period up to 48 hours

Group	0-2 hr	2-6 hr	6-12hr	12-24 hr	24-48 hr
Group P	0	0	6	11	16
Group A	8	14	23	30	33
P value	0.005	<0.001	<0.001	<0.001	<0.001

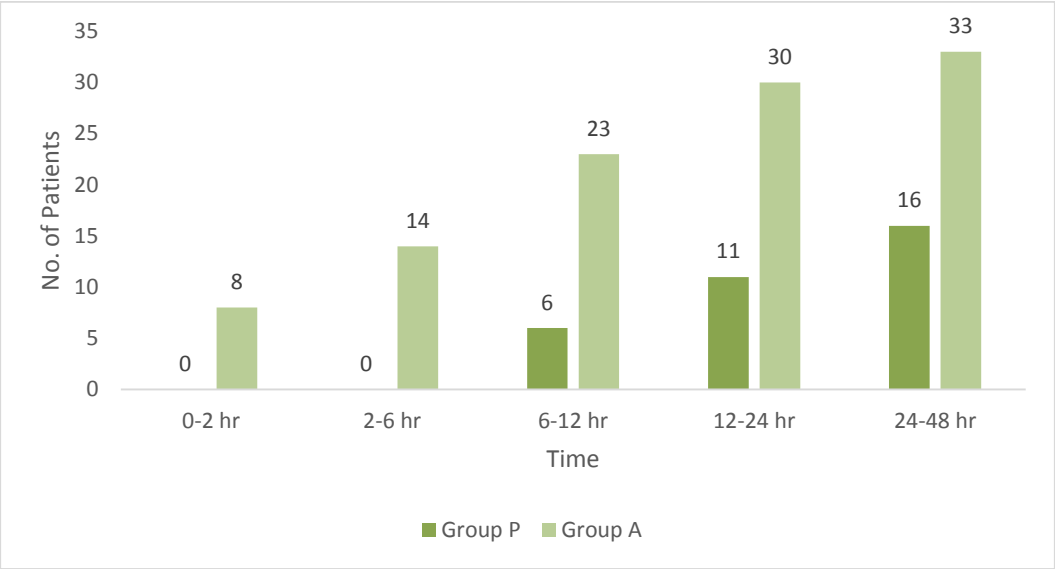

Fig. 2. Incidence of PONV in post operative period up to 48 hours

Mean PISS score in each group has been compared in each Group in the 48 hr period in Table 3 and Fig.3. None of the patients in any group experienced any PONV symptoms at extubation. The mean PISS score in Group P at extubation, 0-2 hr, 2-6 hr, 6-12 hr, 12-24 hr and 24-48 hr were 0, 0, 0, 0.23±0.05, 0.51±0.09, and 0.91±0.13 respectively. The scores at the same times for Group A were 0, 0.23±0.04, 0.46±0.06, 1.34±0.12, 2.63±0.18 and 3.43±0.2 respectively. The mean PISS scores at all times, except for at the time of extubation, was significantly higher in Group A as compared to Group P.

Table 3. Comparison of Mean PISS in 0-48 hours

Time	Group	Mean	Standard Deviation	P value
Extubation	A	0.00	0.00	-
	P	0.00	0.00	
0-2hrs	A	0.23	0.04	<0.001
	P	0.00	0.00	
2-6hrs	A	0.46	0.06	<0.001
	P	0.00	0.00	
6-12hrs	A	1.34	0.12	<0.001
	P	0.23	0.05	
12-24hrs	A	2.63	0.18	<0.001
	P	0.51	0.09	
24-48hrs	A	3.43	0.2	<0.001
	P	0.91	0.13	

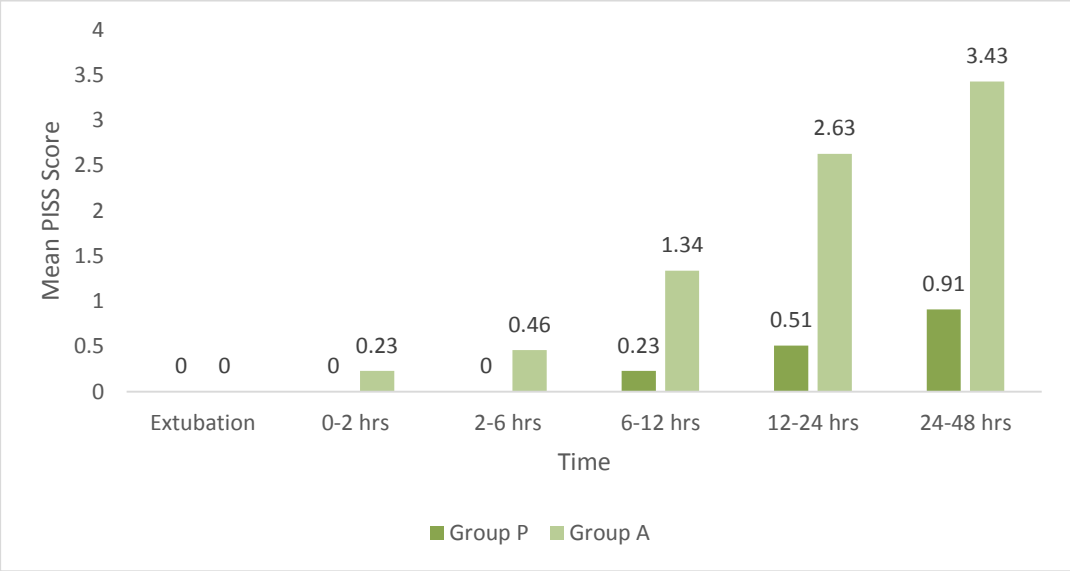

Fig.3. Comparison of Mean PISS in 0-48 hours

Table 4 and Fig.4 depict the number of patients who had complete treatment of PONV (PISS 0) at 48 hrs in each group. 19 patients of Group P and 2 patients of Group A had a PISS score of 0 at 48 hrs post-surgery. Treatment completion was significantly higher in Group P as compared to Group A.

Table 4. Comparison of Treatment completion of PONV in each group

Group	No. of patients with PISS 0 at 48 hours	P Value
Group P	19	< 0.001
Group A	2	

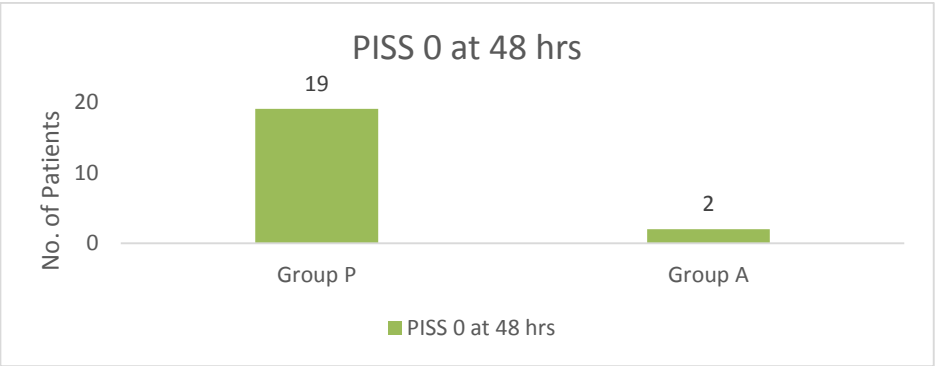

Fig. 4. Comparison of Treatment completion of PONV in each group

The incidence of clinically significant PONV in each group is depicted in Table 5 and Fig. 5. There were 2 patients with PISS score ≥5 in Group P whereas there were 13 patients in Group A with the same score.

Table 5. Incidence of Clinically significant PONV in each group

Group	No of patients with PISS score ≥5	P Value
Group P	2	< 0.001
Group A	13	

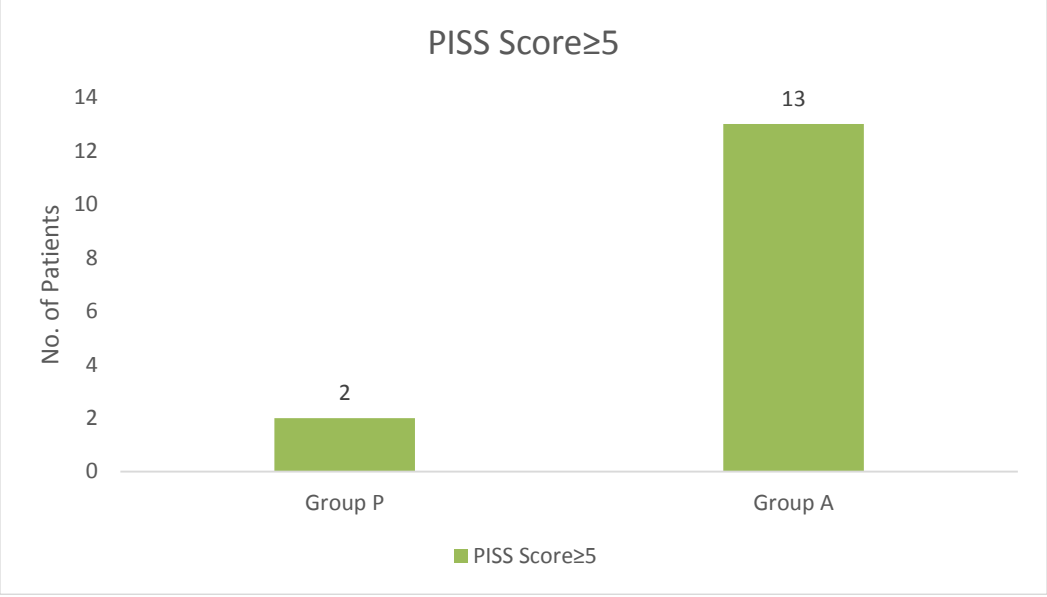

Fig. 5. Incidence of Clinically significant PONV in each group

The requirements for rescue antiemetics for each group has been shown in Table 6. And Fig.6. Two patients from Group P and 13 patients from Group A required rescue antiemetics. Of the 13 patients in Group A, 10 patients were managed with Metoclopramide alone, but 3 patients required both Metoclopramide and Dexamethasone. None of the patients in Group P required Dexamethasone. The requirements for rescue antiemetics was significantly higher in Group A.

Table 6. Rescue antiemetic requirements

Rescue antiemetic requirements	Group		P Value
	Group P	Group A	
Metoclopramide	2	10	< 0.001
Metoclopramide + Dexamethasone	0	3	< 0.001

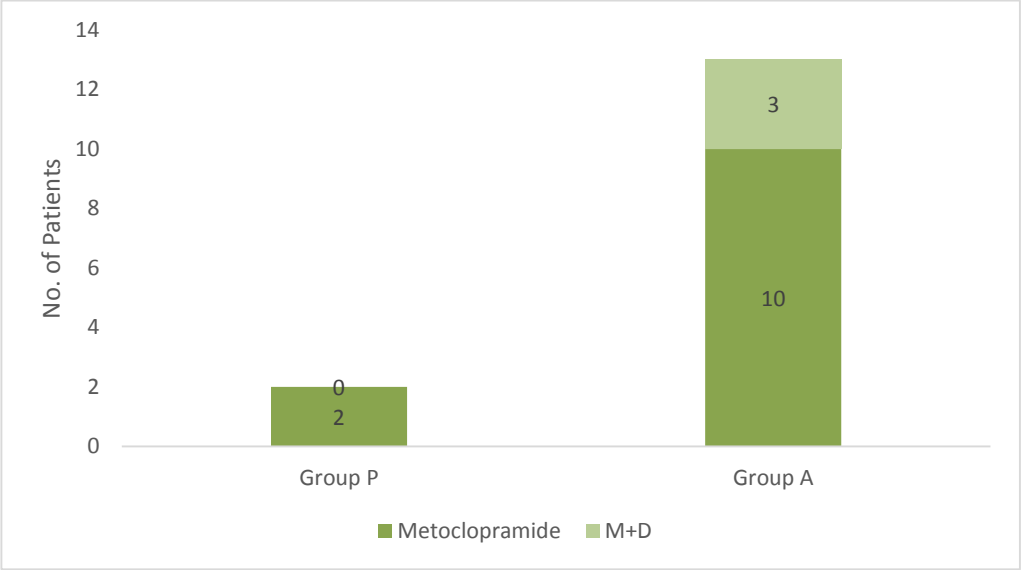

Fig. 6. Rescue antiemetic requirements

Discussion

Nausea and vomiting in the post operative period are a distressing complication following anesthesia, and lead to delays in discharge of the patient undergoing day care surgery. It is the second most common reported complaint following surgery [10]. The search for an effective antiemetic is reflected in the numerous studies that have been carried out so far. Since the mechanism and the pathway involved in nausea and vomiting is complex [11,12], no single drug can serve the purpose of completely preventing nausea and vomiting. The definite risk factors for the incidence of post operative nausea and vomiting include age, gender, duration and the type of anesthesia, obesity, nonsmokers, Meniere's disease, history of motion sickness and history of post operative nausea and vomiting [13,14]. The increased usage of nitrous oxide along with volatile anesthetics in General anesthesia and opioids for post operative analgesia have increased the incidence of post operative nausea and vomiting [15-18].

Currently 5HT3 receptor antagonists are used as first line antiemetic in the prevention of post operative nausea and vomiting. Among serotonin receptor antagonist ondansetron is the first drug of choice. But Palonosetron is superior among them in terms of potency and efficacy. NK-1R antagonists are believed to provide antiemetic activity mainly by suppressing neuron activities at Nucleus tractus solitarius, the central regulator of visceral function [19]. Aprepitant is a highly selective NK-1R antagonist with a half-life of 9 to 14 hours. It has been approved by the FDA for the management of PONV. NK-1R antagonists have shown great antiemetic activities against chemotherapy-induced nausea and vomiting (CINV) [19]. These results encouraged the prophylactic use of NK-1R antagonists to avoid PONV. However, the clinical effects of NK-1R antagonists on PONV prevention remain inconclusive [20,21].

In our study, the efficacy of Palonosetron was compared with Aprepitant in the prevention of postoperative nausea and vomiting in females undergoing Laparoscopic hysterectomy. The risk factor in these subjects are female gender, laparoscopy and gynecological procedures, use of general anesthesia with nitrous oxide and volatile anesthetics and the use of opioids. In the current era of minimally invasive surgery aiming at discharge on the day of surgery, an effective antiemetic with greater potency and longer half-life is required.

Our study group consisted of only females and the comparison of demographic parameters were statistically insignificant among two groups. The incidence of PONV was significantly higher in Aprepitant group in all the time intervals (0-2hr,2-6hr,6-12hr,12-24hr,24-48hr) of observation. The incidence of PONV at the end of 48 hours was (33/35)91.67% in Aprepitant group whereas it was (16/35) 45.71% in Palonosetron group. And the treatment completion rate (PISS<0 at 48 hrs post op) in Aprepitant group was (2/35) 5.7%and (19/35) 54.2% in palonosetron group. The number of patients requiring rescue anti emetic at the end of 48 hours as they were having clinically significant PONV(PISS>4) was (13/35) 37.1% in Aprepitant group where as it was only (2/35) 5.7% in Palonosetron group which concludes that more proportion of patients in the Aprepitant group needed rescue antiemetic.

The Moon Et Al study [7] showed a PONV treatment completion rate of 72.3% (34/47) with Palonosetron and 71.8% (33/46) with Aprepitant. They concluded that Aprepitant has the same PONV prevention effect as palonosetron. Their study subjects were female nonsmokers who received opioids for postoperative pain and were included in the high-PONV-risk group. Despite the risk factors, their study showed a higher PONV treatment completion rate than other studies including ours.

Previous studies have shown a wide range of prevention effects of antiemetic drugs (22.9 − 77.8%), depending on the agent used for PONV prevention in patients indicated for laparoscopic surgery. Park et al. [22] reported a 66% treatment completion rate when palonosetron was administered for PONV prevention in patients indicated for gynecologic laparoscopic surgery, and Jung et al. [23] reported 56% and 63% treatment completion rates in the 80- and 125-mg Aprepitant groups, respectively.

The absorption and distribution of Aprepitant can differ depending on the dose and treatment duration. It takes approximately 3 hours for 40 mg of orally administered Aprepitant to reach its maximum blood concentration [24]. In our study Aprepitant was administered 90 min before anesthesia induction, and the surgery duration differed among patient's average being around 2 hours. So, the maximum blood concentration of Aprepitant might not have been reached in many of the patients at surgery completion which may explain the more incidence of PONV so also more requirement of rescue antiemetic in Aprepitant group during the early post operative period. Whereas there was no incidence of PONV up to 6 hours post operatively in the Palonosetron group and significantly less incidence after 12 hours post op which may be explained as it was administered in i.v formulation and having a long duration of action, i.e,40 hours. The

incidence of PONV was still significantly higher in the Aprepitant group from 6 hours to upto 48 hours, with increased requirement of rescue antiemetics.

Conclusion

Palonosetron 0.075 mg iv was found to be superior to Aprepitant 40 mg oral dose in the prevention of post operative nausea and vomiting in patients undergoing laparoscopic hysterectomy under general anesthesia.

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