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A Prospective Single Blind Randomized Study on Prevention of Postoperative Nausea and Vomiting with Palanosetron versus Ondansetron in Patients undergoing Laparoscopic Surgery

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Abstract

Context: In the modern era of surgical field laparoscopic surgeries are more frequently performed than open surgeries. Postoperative nausea and vomiting is a common complaint encountered in the patients who have undergone laparoscopic surgeries because of pneumoperitoneum created by CO_2. A number of anti-emetics are given as prophylactic agents to prevent postoperative nausea and vomiting. Among them 5-hydroxytrypatmine type 3 receptor antagonists are highly effective in prevention and treatment of PONV. With this background we conducted a study for evaluating the effectiveness of two 5-HT_3 receptor antagonists in prevention of PONV in patients undergoing laparoscopic surgeries under general anesthesia. *Aim:* To compare the efficacy and safety profile of two 5 HT_3 antagonists namely palonosetron and ondansetron in the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgeries. *Settings & Design*: This was a prospective, randomized, single-blind comparative study. Sixty patients of age group between 18-60 years of American Society of Anaesthesiologists physical status class I and II undergoing laparoscopic surgeries were enrolled. They were randomly allocated into two groups namely Group A and B with 30 patients in each group. Group A received 0.075mg of injection palonosetron and Group B received 4mg of injection ondansetron intravenously 30 minutes before induction of anaesthesia. *Statistical Analysis used*: Statistical work up was performed using the SPSS version 16. Student's t –test was used for quantitative data and Chi- square test was used for qualitative data. P value of less than 0.05 was found to be statistically significant. *Results*: The incidence of PONV in group A (palonosetron) was found to be 13% which is lesser than group B (ondansetron) where the incidence was 23%. The need for rescue antiemetic was also comparatively lesser in group A than group B. (23% vs 51%). The number of complete responders were 26 (86%) and 23 (76%) for palonosetron and ondansetron respectively. *Conclusion:* Palonosetron is effective antiemetic for preventing PONV during the late postoperative period while compared to ondansetron.

Keywords: Palonosetron; Ondansetron; Postoperative Nausea and Vomiting; Laparascopy.

Introduction

Nausea and vomiting in the postoperative period is the second most common complaint reported next to pain (which is the most common) [1-7]. Postoperative nausea and vomiting (PONV) occurs in 20-30% of surgical patients [8]. PONV can be such an unpleasant experience that patients often rate it worse than postoperative pain [9]. While the experience of PONV is generally self-limited, postoperative vomiting/retching can lead to rare but serious medical complications such as aspiration of gastric contents, suture dehiscence, esophageal rupture etc [10,11]. PONV may delay patient discharge from postanesthesia care unit (PACU) and can be the leading cause of unexpected hospital admission after ambulatory anesthesia [12].

Serotonin (5-HT_3) receptor antagonists exert their effects in the chemoreceptor trigger zone and at vagal afferents in the gastrointestinal tract. They are not only the most commonly used antiemetics for prevention but also the most commonly used

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antiemetics for rescue treatment [13]. One reason may be that serotonin antagonists are currently the only class of intravenously available antiemetics that may have a rapid onset for rescue treatment while being without sedative side effects. As mentioned previously, serotonin antagonists are highly selective and tend to block almost all receptors. Ondansetron was the first of this class of drug to be marketed; others include dolasetron, tropisetron and granisetron and palanosetron. In 2003, an expert panel agreed that there was no evidence of any difference in the efficacy and safety profiles of the different 5-HT_3 antagonists in the prophylaxis against PONV [14].

Ondansetron was the first serotonin antagonist, and its introduction was a milestone in the prevention of early chemotherapy induced nausea and vomiting. Given its superior efficacy for chemotherapy induced nausea and vomiting, it is not surprising that ondansetron quickly established a reputation as the most effective antiemetic for prevention of PONV. Whereas all serotonin antagonists have generally been considered to be similarly effective, palanosetron might be an exception, not only because of the long half-life of about 40 hours but also because it seems to be able to prevent delayed chemotherapy induced nausea and vomiting for which serotonin antagonists are usually not effective. Whether this will translate into higher efficacy for the prevention of PONV, and perhaps postoperative nausea and vomiting, has yet to be shown. With this background we conducted a study for evaluating antiemetic efficacy of ondansetron and palonosetron in patients undergoing major laparoscopic surgery.

Materials and Methods

It was a prospective, randomized, single blind study conducted at our Institution after Ethical Committee approval. A single pre-induction intravenous dose of palonosetron (0.075mg fixed dose) or ondansetron (4mg fixed dose) was administered to 60 patients aged between 18-60 years undergoing laparoscopic surgeries. A written informed consent was obtained from all subjects prior to recruitment.

Exclusion Criteria

- Pregnancy
- BMI >30 Kg/ m^2
- Distinct spells of nausea, vomiting or retching within 24 hours prior to surgery
- Use of corticosterioids, psychoactive drugs or any other medications with known emetic or antiemetic effect within 24 hours prior to surgery
- Chronic kidney or liver disease

Randomization was done using computer generated random number list and allocation was concealed till the point of drug administration using serial number opaque sealed envelopes. The study drug was administered in a single blind manner, taking care to ensure that the patient was not aware of the exact identity of the antiemetic drug that she received, either before or during the 24 hours observation period following surgery. The study medications were prepared and given 30 minutes before induction of anesthesia in the preoperative holding room. Patients received either palonosetron 0.075mg IV or ondansetron 4 mg IV, as per the randomization code. The other pre-anesthetic regimen and anesthesia procedure were uniform for all subjects. On arrival in the operation theatre , routine monitoring devices were connected, including non-invasive arterial pressure, ECG and pulse oximetry. General anesthesia was administered to the patient with cuffed endotracheal intubation as per routine protocol. Anesthesia was induced with propofol 2mg/kg and fentanyl citrate 2mcg/kg and tracheal intubation was done with atracurium besylate 0.6mg/kg body weight. Propofol was preferred for induction due to its favorable recovery like rapid emergence and reduced PONV. Anesthesia was maintained with atracurium besylate and sevoflurane 1-2% in N_2O-O_2 mixture to maintain muscle relaxation and depth of anesthesia respectively. Intraoperative analgesia was achieved with intermittent bolus of fentanyl citrate. After the end of procedure, patient was reversed with neostigmine and glycopyyrolate. Intra-abdominal pressure was kept between 10-15mmHg. Gastric decompression was done with Ryle's tube insertion as when needed. Ini.Paracetamol 1gm was given as postoperative analgesic intravenously.

For the purpose of the study, an episode of PONV denoted either a distinct spell of nausea, retching (an involuntary attempt to vomit but not actually productive of stomach contents) or vomiting (actual expulsion of stomach contents). The primary outcome measure was the total number of PONV episodes in the 24hrs period following surgical procedure

The secondary outcome variables were:

- Frequency of nausea, retching and vomiting episodes individually in the 24hrs period following the surgical procedure.

- Use of rescue antiemetic medication (Metoclopramide 10 mg slow intravenous injection).
- Number of complete responders – no emetic episodes and no rescue medication.
- Overall satisfaction with the nausea-vomiting experience on a four-point Likert scale (Unsatisfied, neutral, satisfied, and highly satisfied) at 24hrs after surgery completion.

Hemodynamic variables such as heart rate, blood pressure and SpO2 were monitored at regular intervals and adverse effects related to the administered study drugs were also recorded.

Results

Sample size was calculated to the primary outcome (Patients with complete response). Statistical analysis was performed using SPSS version 16. Quantitative data were represented as mean and SD. Qualitative data were presented as number and percentage. Tests used were Student's t-test for analysis of age, weight, duration of surgery and nausea score and Chi square test for analysis of categorical variables. P-value less than 0.05 was considered statistically significant.

The patient demographic profile such as age, sex, ASA physical status and weight were quiet comparable and found to be statistically insignificant. In group A, three patients had previous h/o PONV and 5 patients in group B. All patients received opioids intraoperatively. In the postoperative period, most of the patients (22 {73%} in group A and 19 {63%} in group B) received opioids for pain relief. There was no statistical difference in PONV while comparing with the choice of antiemetic used. The duration of anesthesia, surgery and CO_2 insufflation were comparable between the two study groups and found to be statistically insignificant.

The incidence of PONV was comparatively higher in ondansetron group of patients (23%). The time to rescue antiemetic usage was found to be prolonged in palanosetron group of patients (13%). Patient satisfaction score based on Likert scale was comparatively higher in group A patients those who had received palanosetron as the prophylactic antiemetic preoperatively. The number of complete responders are greater in group A than group B. More than 70% of patients were satisfied. The side effect profile of both drugs were comparable. None of the study patients experienced headache, dizziness etc in the postoperative period.

Table 1: Demographic Profile

Characteristics	Group A (Palanosetron) (n=30)	Group B (Ondansetron) (n=30)	p Value
Age (in years)	39±12.15	38.10±13.41	0.7785
Male/Female	21/09	17/13	
ASA I/II	18/12	16/14	
Weight (in Kg)	60.37±7.97	60.30±8.14	0.8357
Previous H/o PONV/Motion Sickness	03 (10%)	05 (16.66%)	

Table 2: Perioperative details

Characteristics	Group A (Palanosetron) (n=30)	Group B (Ondansetron) (n=30)	p Value
Opioid Usage			
Intraoperative period	30 (100%)	30 (100%)	
Postoperative period	22 (73.33%)	19 (63.33%)	
Duration of anesthesia (in minutes)	80.70±16.90	80.50±17.56	0.9643
Duration of surgery(in minutes)	75.13±16.07	76.23±16.77	0.7963
Duration of CO_2 insufflation (in minutes)	69.12±15.87	70.32±16.13	0.8471

Table 3: Patient satisfaction survey based on Four Point Likert Scale

Characteristics	Group A (Palanosetron) (n=30)	Group B (Ondansetron) (n=30)
Unsatisfied	1 (3%)	3 (10%)
Neutral	3 (10%)	7 (23%)
Satisfied	22 (73%)	20 (67%)
Highly satisfied	4 (13%)	0

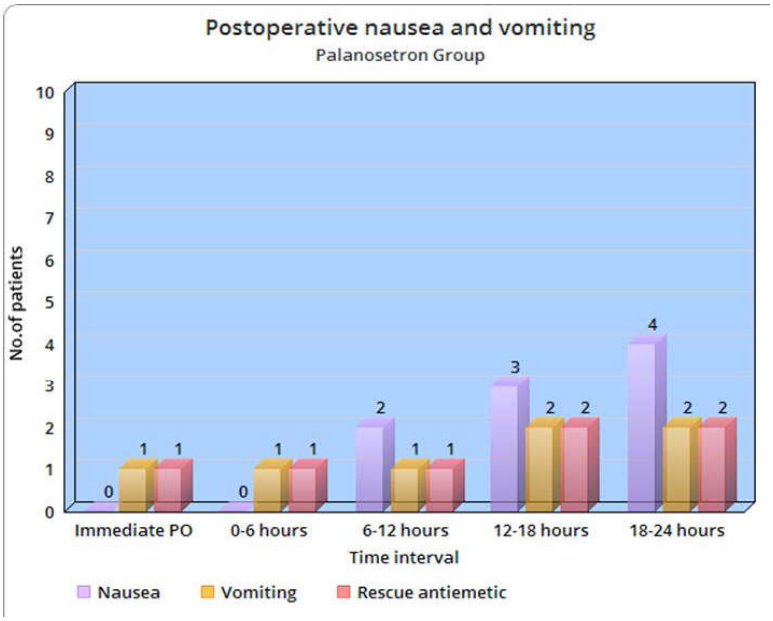

Fig. 1:

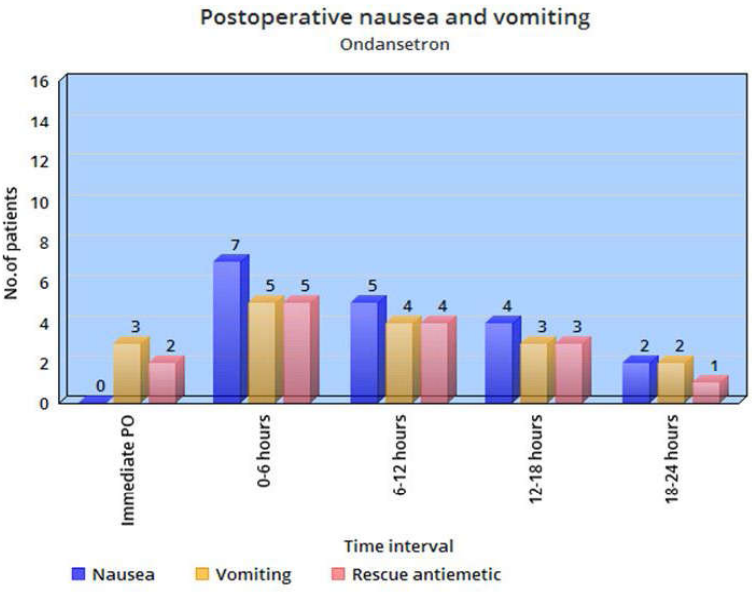

Fig. 2:

Discussion

Nausea (from the Greek *nautia* meaning "seasickness") is often described as a "sensation of unease and discomfort in the stomach with an urge to vomit". Nausea may manifest at different intensities, may last a variable period of time, and may be waxing and waning (cyclic change in intensity over time). There are three ways to assess the intensity of the symptoms namely Numerical rating scale, Verbal rating scale and Visual analogue scale.

Vomiting, as a clinical symptom, is the forceful expulsion of gastric contents through the mouth or nose. Retching is similar to vomiting with the exception that no gastric contents enter the pharynx. An *emetic episode* is often operationally defined as one or more instances of vomiting and/or retching is separated by no more than 1 minute of respite. However, for the sake of simplicity and because vomiting is much more frequent than retching, many authors reports of vomiting will include both vomiting and retching. In such instances, use of the term 'emetic episode' is preferable. The measurement of vomiting and emetic episodes is simpler than that of nausea because the former involves a distinctive and recognizable muscular reflex. Severity is therefore best evaluated by number of episodes, and recording of the times of each individual episode allows secondary analysis with regard to the time course.

PONV is influenced by multiple patient, surgery and anesthesia related factors and requires release of 5-HT in a cascade of neuronal events involving both the central nervous system and gastrointestinal tract. The 5-HT subtype 3 receptor participates selectively in the emetic response. The use of anti-emetics, either alone or in combination, remains the mainstay in PONV management. Drugs used include metoclopramide, haloperidol, dexamethasone and the selective 5-HT_3 receptor antagonists. The last group is now a first line option because of effectiveness and lack of adverse drug reactions [15,16]. Most clinical research with the 5-HT_3 antagonists has used ondansetron and its antiemetic efficacy is well established in chemotherapy induced emesis and in the treatment and prevention of PONV. However, several alternatives to ondansetron (e.g. granisetron, tropisetron, dolasetron, ramosetron) are now available. Palonosetron, approved by the Drugs Controller General of India is the most recently introduced member of this class of drugs in India. Its interaction pattern with the 5-HT_3 receptor is different from earlier 5-HT_3 receptor antagonists, enabling a higher binding affinity and longer half-life [17].

Palonosetron has been compared with placebo for the prevention of PONV in patients undergoing laparoscopic surgeries. Comparison with other antiemetic drugs and in other types of surgery is still limited. We therefore evaluated the antiemetic effectiveness of palonosetron (0.075mg fixed dose) by comparing with ondansetron (4mg fixed dose) in patients undergoing laparoscopic surgeries using a single dose pre-induction intravenous injection.

In our study we found the incidence of PONV in both study groups was quiet comparable. In group A (palanosetron) the incidence of PONV was found to be 13%. Among ondansetron group the incidence was found to be 23%. And this result was found to be statistically significant. In palanosetron group most of the patients who experienced PONV was found to be maximum between 12-18 hours. But in patients who received ondansetron experienced nausea and vomiting between 0-6 hours. This reveals the fact that palanosetron is a long acting antiemetic (5-HT_3) while compared with ondansetron. The results of our study were quiet comparable with other studies done by Swaika S et. al [19]. In the study done by Candiotti et.al, incidence of PONV was found to be 26% and 51% between 0-24 hours and 24-48 hours in patients who received palonosetron 0.075 mg while compared to placebo group before the induction of anesthesia. This result was quiet comparable with other our study.

The study done by Swaika S et. al [19] for finding out a better choice of antiemetic to prevent PONV in patients undergoing laparoscopic cholecystecomy. They compared ondansetron, ramosetron or palonosetron. The number of complete were 65.5% for ramosetron, 37.9% for palonosetron and 34.5% for ondansetron, representing a comparison between ondansetron and palonosetron showed a marginal difference between the two antiemetics. Their study revealed the fact ramosetron 0.3mg was effective than palonosetron 0.075mg and ondansetron 8mg in the early postoperative period.

In the present study the need for rescue antiemetics was found to be higher among ondansetron group between 0-6 hours which shows the efficacy level. In group A 23% of patients had received rescue antiemetic during the first 24 hours. And 51% of patients received rescue antiemetic during the study period. The rescue antiemetic used in our study was inj.metaclopramide 10 mg slow intravenous. This was given when retching or vomiting occured or on patient's demand. This result is not consistent with Bhattacharjee et.al in which no rescue antiemetic was required in both study group. In the study done by Candiotti et. al [20] nearly 52% of patients required rescue antiemetic in placebo group and 44% in palonosetron group. Kovac et. al found in their study the need for rescue antiemetic was found to 46% and 27% in placebo and palonosetron group.

The usage of opioids in the postoperative period increases the risk for PONV in a dose dependent manner. This effect can be continued as long as opioid usage in the postoperative period. Since laparascopic procedures are at maximum of producing nausea and vomiting due to gaseous distention. So we supplemented with paracetamol injection for postoperative pain relief to minimize opioid consumption for all study participants. Adverse effects of the study drugs namely palonosetron and ondansetron are headache, dizziness and drowsiness. Adverse effects with prophylactic dose of palonosetron and ondansetron were not statistically significant. The incidence of headache and dizziness was found to be 6% and 9% in group A and group B respectively. This result was quiet similar to the study done by Bhattacharjee et. al [21].

The overall satisfaction score of palonosetron group was highly significant while comparing with ondansetron group. Nearly 70% of patients were satisfied with prophylactic antiemetic received as palonosetron before induction of anaesthesia. And 10% of patients were highly satisfied with the drug they received pre induction. This is quiet comparable with ondansetron group.

Our study revealed the fact the antiemetic efficacy of palonosetron is significantly better in its antiemetic efficacy while compared to ondansetron especially after 12-24 hours. During the 12-24 hours the usage of rescue antiemetic was significantly low. The exact reason is not clearly known but it may be due to prolonged half life of palonoseton 40 hours. Palonosetron interaction with 5HT-3 receptors in an allosteric, positively cooperative manner at sites different from that for ondansetron.

Limitation of our Study

Our study has some limitation. The duration of study was restricted to 24 hours postoperative period. So we were not able to the study the full efficacy of palonosetron in the extended postoperative period upto 48 hours since it's half life is 40 hours which is comparatively higher than other 5HT-3 antagonists.

Conclusion

For the prevention of postoperative nausea and

vomiting following laparoscopic surgeries, 5HT-3 antagonists were found to be highly efficacious. Among them palonosetron was found to be quiet safe and longer acting antiemetic drug that can be administered in the recommended dosage of 0.075mg before induction of anesthesia. Hence palonosetron 0.075 mg is a better choice of antiemetic in the late postoperative period following laparoscopic surgeries.

Acknowledgement

None declared

Conflict of Interest

Nil

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