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"Palonosetron vs Ondansetron for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: A comparative study"

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Abstract:

Background: *Postoperative nausea and vomiting (PONV) is commonly seen after laparoscopic surgery. In this study, we investigated and compared the efficacy of palonosetron and ondansetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy.*

Aims & Objectives: *To compare the efficacy of palonosetron vs ondansetron in long term prevention of PONV, incidence of complete response, need of rescue antiemetic treatment and overall patient's satisfaction.*

Methods: *A prospective, randomised,interventional study was conducted in M.L.N. Medical College, Allahabad comprising 90 patients undergoing elective laparoscopic cholecystectomy, who were randomly allocated to either palonosetron group (n = 45) or the ondansetron group (n = 45). Palonosetron 75 μg or ondansetron 8mg was injected as a bolus before the induction of anaesthesia in their respective groups. The incidences of PONV at 0-6hrs, 6-12hrs, 12-24 hrs, incidence of complete response, need of rescue antiemetic treatment and overall patient satisfaction were recorded postoperatively.*

Results: *Post operative nausea was significantly less in palonosetron group in late post- operative period in 12-24 hrs (33.33% vs 13.33%, p value 0.046) as well as overall 0-24 hrs (55.55% vs 28.88%, p value 0.0189 respectively). Patients showing complete response were significantly higher in palonosetron group (31.11% vs 64.44%, p value 0.031) and the need for rescue antiemetics was also less (22.22% vs 4.44%, p-value 0.0266). Other parameters such as early PONV, overall patient satisfaction, and adverse effect profile were comparable between both the groups.*

Conclusion: *Palonosetron is more effective than ondansetron for prevention of post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy.*

Keywords: *PONV, Ondansetron, Palonosetron, Laparoscopic cholecystectomy.*

I. Introduction

Postoperative nausea and vomiting (PONV) is often the most common complication following anaesthesia and surgery[1]. PONV has been characterised as the "big little problem" by **Kapur (1991)[2]**.

PONV encompasses a triad of signs and symptoms. Nausea is described as a "subjective unpleasant sensation associated with the awareness of the patient to vomit". While vomiting is "the actual physical phenomenon of forceful expulsion of gastrointestinal contents from the mouth". It thus includes not only physical signs (i.e. retching and vomiting) but also the unpleasant subjective feeling (nausea) experienced by the patient. In high-risk patients, the incidence of PONV can reach upto 80%, indicating the importance of prophylaxis and control of this distressing complication**. [3]**

Several receptor types – including serotonin 5HT3, dopamine D2, histamine H2, α2-adrenergic, muscarinic cholinergic, neurokinin 1 and GABA- are involved in the ignition and co-ordination of the vomiting reflex in patients with PONV**. [4]**

Laparoscopic surgery is one condition, where risk of PONV is particularly high. The incidence of PONV has been reported high (25% - 42%) with no antiemetic treatment in patients undergoing laparoscopic cholecystectomy. This increased risk of PONV is due to pneumo-peritoneum causing stimulation of mechanoreceptors in the gut.

The use of antiemetics, either alone or in combination, remains the mainstay in PONV management. Drugs used include anticholinergic drugs (scopolamine, atropine), dopamine antagonist drugs (metoclopramide, promethazine, prochlorperazine), haloperidol, steroids (dexamethasone) and the selective 5-HT3 receptor antagonists (ondansetron ,granisetron , palonosetron). The last group is now a first line option because of effectiveness and general lack of adverse drug reactions.**[5,6]**

The present randomized, double-blind study was designed to compare the efficacy of palonosetron vs ondansetron as prophylactic regimens for the prevention of PONV after laparoscopic cholecystectomy with known high-risk of PONV.

II. Patients and methods

The present prospective, randomised, double blinded, non-placebo controlled study was conducted in the Dept. of Anaesthesia & Critical Care, S.R.N. Hospital, M.L.N. Medical College, Allahabad over a period of August 2014 to August 2015. The present study was approved by the ethical committee of the institution and a written informed consent was taken from the patients after explaining to them in detail about the implications of the anaesthetic and the surgical procedure.

The study included 90 patients between 18-60 years of age, of either sex, of ASA physical status I & II, scheduled for elective laparoscopic cholecystectomy. Patients were excluded from the study if they had received antiemetics, steroids or psychoactive medications within 24 h of study initiation. Patients with vomiting or retching in the 24 h preceding surgery, those who had received cancer chemotherapy within 4 weeks or emetogenic radiotherapy within 8 weeks before study entry, and patients with ongoing vomiting fromgastrointestinal disease were excluded.

Study design and treatment

Patients were randomised to be allocated to either Ondansetron or Palonosetron group of 45 patients each.All patients were pre-medicated with oral alprazolam (0.25mg) and ranitidine (150mg) night before surgery, and were advised NPO for 8hrs. Depending upon the group allocated, patients received Palonosetron 75µg or Ondansetron 8mg, diluted upto 10ml with normal saline, given slowly intravenously as bolus dose 5min before induction of anaesthesia.

A standardized protocol for general anaesthesia was followed for all the patients.

All patients were given Inj. midazolam 0.01mg/kg i.v.& Inj. Fentanyl 2microgm/kg, & Inj. Glycopyrolate 0.01mg/kg intravenously just before induction of anaesthesia. All patients were pre-oxygenated for 3 minutes with 100% oxygen.

The patients were induced with Inj. Propofol 2.5mg/kg i.v. and tracheal intubation was facilitated with Inj. Succinylcholine 2mg/kg i.v. 1minute after its administration.

Anaesthesia was maintained with Oxygen and Nitrous oxide mixture (40%:60%) and repeated dose of long acting muscle relaxant of non- depolarising type vecuronium.Residual neuromuscular blockade of vecuronium is reversed with Inj. Neostigmine (0.05mg/kg) and Glycopyrolate (0.01mg/kg).

No other sedative or antiemetic drug was administered.

During the operative period, duration of anaesthesia and surgery were also recorded.

The post-operative rescue analgesia was standard for all and was provided with inj.diclofenac sodium 75mg.

Patient monitoring

Episodes of post-operative nausea, vomiting and retching experienced by the patients within first 24hrs of anaesthesia i.e. during 0-6hrs, 6-12hrs, 12-24hrs and 0-24hrs, and the incidence of complete response were recorded. No distinction between vomiting and retching (i.e. retching event was considered as a vomiting event) was made.

Complete response of prophylactic antiemetic is defined as no post-operative nausea and vomiting and no need for rescue antiemetic medication in post-operative period of 24hrs after anaesthesia.

Rescue antiemetic was given with metoclopramide 10mg intravenous injection only when patient experienced nausea for 3minutes or more than one episode of PONV occurred, and its incidence was recorded.

Overall patient's satisfaction on Three-point scale as Satisfied, Neutral or Dissatisfied, and the incidence of Adverse effects (like dizziness, headache, constipation,drowsiness) were also recorded.

Statistical analysis

Sample size was calculated by a power analysis while designing the study- allowing an α-error of 5% and a β-error of 20%, it was estimated that a minimum of 42 patients per group would be required to show a 30% difference in the incidence of PONV. All statistical analysis were performed using GraphpadInstat software, version 3.10, 32 bit for windows. Numerical variables were compared between groups by Student's t-test. χ^2 with Yates' correction or Fisher's exact test was employed for intergroup comparison of categorical variables. All analysis were two tailed. Statistically significant implied $p<0.05$.

III. Result

In total, 90 patients were recruited, all of them completed the study. Baseline demographic profile and clinical characteristics were comparable between both the groups with no statistically significant difference

between them (p-value>0.05).

Table 1-Baseline demographic profile and clinical characteristics

	ONDANSETRON GROUP (n=45)	PALONOSETRON GROUP (n=45)	p-VALUE
Male/Female	8/37	5/40	0.55
AGE in years (mean±SD)	39.86 ±9.353	43.22 ±8.541	0.0786
WEIGHT in kg (mean±SD)	54.62 ±6.779	55.46 ±5.383	0.5168
ASA GRADE I/II	36/9	38/7	0.7836
RISK FACTORS History of PONV and/or motion sickness Non-smoker	 13(28.88%) 38(84.44%)	 11(24.44%) 41(91.11%)	 0.8116 0.5216
DURATION OF ANAESTHESIA in mins (mean±SD)	102.0 ±10.198	100.2 ±12.017	0.4457
HEART RATE per min (mean±SD)	83.47 ±7.325	82.31 ±6.782	0.4378
ARTERIAL PRESSURE in mmhg (mean±SD)	90.75 ±6.997	89.2 ±6.240	0.2704

The incidence of nausea was significantly lower in the palonosetron group than in the ondansetron group during the 12-24h andoverall 0– 24 htime interval (p<0.05, Table2). The frequency of vomiting was also less during the 12-24h and overall 0– 24 h time interval although not statistically significant.

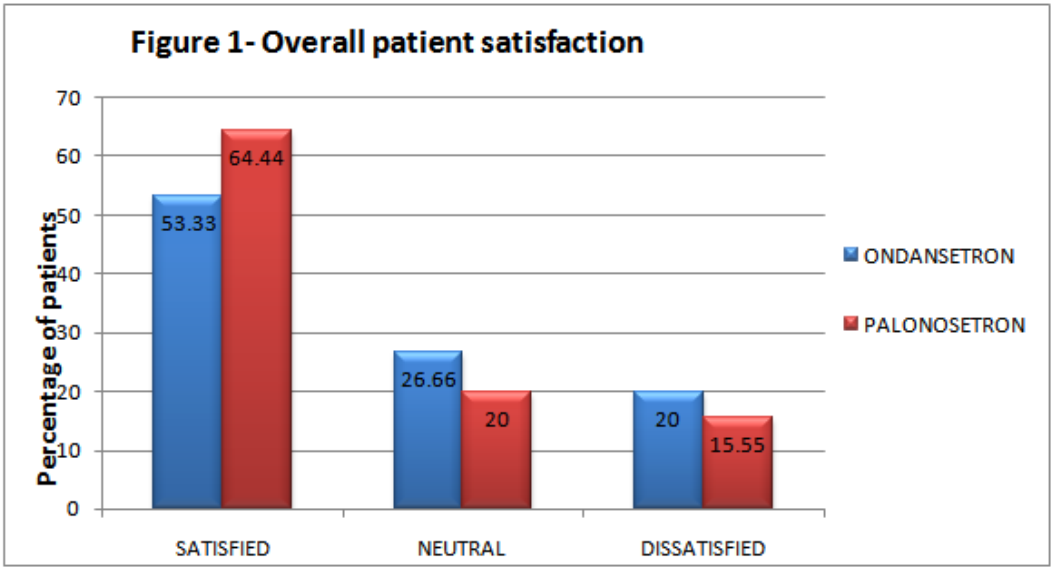
Table 2.Comparison of frequency of PONV in post-operative period

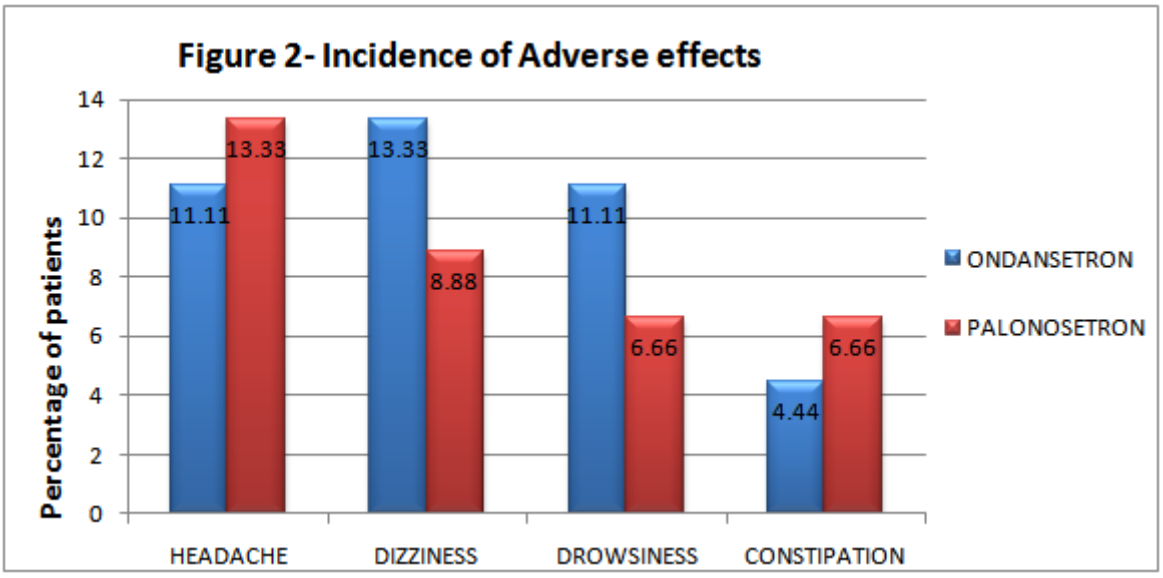
Post-operative period		ONDANSETRON (n=45)	PALONOSETRON (n=45)	p- VALUE
0-6 hours	NAUSEA	8 (17.77%)	5 (11.11%)	0.5487
	VOMITING	2 (4.44%)	1 (2.22%)	1.000
6-12 hours	NAUSEA	10 (22.22%)	3 (6.66%)	0.069
	VOMITING	3 (6.66%)	1 (2.22%)	0.6164
12-24 hours	NAUSEA	15 (33.33%)	6 (13.33%)	**0.0462**
	VOMITING	4 (8.88%)	2 (4.44%)	0.6766
0-24 hours	NAUSEA	25 (55.55%)	13 (28.88%)	**0.0189**
	VOMITING	7 (15.55%)	4 (8.88%)	0.5216

Complete response (no PONV and no rescue antiemetic)was more in the palonosetron group compared with the ondansetron group and the need for rescue antiemetics was less during 0 – 24 h time interval (p<0.05) (Table 3). Incidence of adverse effects (Fig. 1)and patient satisfaction (Fig.2) were comparable between the two groups.

Table 3-Incidence of Complete Response and need for Rescue Anti-emetics

	ONDANSETRON (n=45)	PALONOSETRON (n=45)	p-VALUE
COMPLETE RESPONSE	14(31.11%)	29(64.44%)	**0.031**
RESCUE ANTIEMETICS	10(22.22%)	2(4.44%)	**0.0266**





IV. Discussion

A significant proportion of patients experience PONV despite the widespread use of prophylactic antiemetics, including 5-HT3 receptor antagonists.[7]5HT3 receptor antagonist have an enviable safety profile, with minor side-effects and rare cardiac conduction abnormalities. Ondansetron was the first 5-HT3 receptor antagonist to be marketed and has frequently been used to control PONV.[8]Palonosetron – a second generation 5-HT3 antagonist – has unique structural, pharmacological and clinical properties that distinguish it from other 5-HT3 antagonists.[9]It is the most recently introduced member of this class of drugs in India. Ithas a greater binding affinity and longer half-life (40hrs) than older 5-HT3 antagonists. The present study was carried out mainly to see the see the comparative efficacy of the new and much promising long-acting 5-HT3 antagonist palonosetron against ondansetron in prevention of PONV in patients undergoing laparoscopic cholecystectomy.

In our study, the dose selection for palonosetron was based on the studies of **Candiotti *et al.*[10]**, the minimum effective dose of palonosetron in the prophylaxis of PONV is 0.075 mg, and this has been approved by the food drug agency (FDA).US Food and Drug Administration (FDA) also approved a single dose of palonosetron 0.075 mg for preventing PONV for up to first 24 hours after the surgery.[8,11]

A meta-analysis by **Tramer*et al.*[12]** suggested that an 8 mg dose of ondansetron was optimal for the prevention of PONV.

The incidence of PONV is associated with many factors like age and gender (female gender, younger age increase the risk of PONV),history of motion sickness or PONV, smoking status (smoking decreases the risk of PONV), postoperative opioid use, type and duration of surgery, anaesthesia and ambulation.[1,13,14] These factors were comparable between both groups in the present study.

In the present study, palonosteron 0.075 mg was more effective at reducing PONV than ondansetron 8 mg. This could reflect the high receptor affinity of palonosetron for 5-HT3, with a low affinity demonstrated for other receptors and the longer duration of action.[4,15]

V. Conclusion

From the present study it may be concluded that Palonosetron is more effective than Ondansetron for prevention of PONV in patients undergoing laparoscopic cholecystectomy. It has lesser PONV in late post-operative period as well as overall 0-24 hours. Also the need for rescue antiemetics is significantly less and incidence of complete response higher with the use of palonosetron. The overall patient satisfaction and adverse effect profile were comparable between both the groups.

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