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Effect of Palonosetron on Prevention of Post-Operative Nausea and Vomiting as Compared to Granisetron in Female Patients undergoing Laparoscopic Surgery

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Abstract

Background & Objectives: Post-operative nausea and vomitting is the second major problem in the post-operative period that causes patients much discomfort by itself and by prolonging the patients, stay in the hospital. In the present scenerio incidence of PONV has reduced to 20-30% due to refined techniques of anaesthesia, proper pre-operative preparation and by heeding the risk factors. However it remains a big problem. This study evaluates the protection offered by Palonosetrone and Granisetrone in the prevention of PONV in female patients undergoing laparoscopic surgery under general anaesthesia. *Materials and Methods:* Total ninety-six premenopausal female patients (forty eight in each group) of aged ≥ 18 years of age of ASA class I/II and posted for gynaecological laparoscopic surgery under general anaesthesia were enrolled in this randomised, prospective, single blind, comparative, clinical trial. Group P received Inj.Palonosetrone 0.075mg and Group G received Inj.Granisetron 2.5 mg intravenously one minute before induction of anaesthesia. All episodes of PONV (complete response, nausea, retching, vomiting, emetic episode) were recorded for 0-3 hours in post-anaesthesia care unit and for 3-48 hours in postoperative ward. *Results:* All the parameters and variables studied were subjected to statistical analysis using Chi-square test and unpaired student 'T' test. During 0-24 hours, the incidence of nausea and vomiting were comparable in both the groups. whereas, between 24-48 hours, incidence of nausea and vomiting was significantly high in Group G as compared to Group P($p<0.01$). *Conclusion:* prophylactic single intravenous dose of palonosetron 0.075mg is more effective than granisetron 2.5mg for controlling postoperative nausea and vomiting between 24-48 hours post operatively with less incidence of side effects.

Keywords: Palonosetrone; Granisetrone; Post Operative Nausea Vomiting (PONV).

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Introduction

Post operative nausea and vomiting (PONV) is one of the common postoperative complications that occur after surgery performed under general anaesthesia. Female patients, obese patients, patients with history of motion sickness, pregnant patients, patients with full stomach and patients undergoing surgeries like Gynecological, middle ear, laparoscopic, and ophthalmic surgery have more risk of PONV [1]. The incidence of post operative nausea-vomiting after laparoscopic surgery is high (40%-75%). PONV though generally self-limiting and not very serious, may lead to dehydration and electrolyte imbalance if it is persistent, aspiration of gastric contents especially in patients with reduced consciousness and disruption of surgical repair. It

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also delays recovery, prolongs hospital stay and increases costs due to additional drug usage [2]. Anaesthetic strategies to prevent vomiting include using regional anaesthesia wherever possible, avoiding emetogenic anaesthetic drugs and use of prophylactic antiemetic drugs.

Various pharmacological agents (antihistamines, prokinetics, phenothiazines, butyrophenones, dopamine receptor antagonists) have been tried for the prevention and treatment of PONV but untoward side effects such as excessive sedation, hypertension, dry mouth, dysphoria, hallucination, and extrapyramidal symptoms have been noted [3]. 5 hydroxytryptamine type 3 (5HT3) receptor antagonists are devoid of such side effects and they are particularly effective in controlling the nausea and vomiting produced by cancer chemotherapeutic agents and they are considered the gold standard for this purpose [4]. However, Candiotti et al. and Kovac et al. [5] studied their role in prevention of post operative nausea vomiting (PONV). Ondansetrone, Granisetrone, Dolasetrone, Tropisetrone and ramosetrone are first generation 5 HT 3 receptor antagonists.

The disadvantages with first generation 5 HT 3 receptor antagonists especially ondansetrone are its short half life so requiring frequent dosing. Also, ondansetrone is prone to cause ECG changes in the form of prolongation of QTc interval and cardiac arrythmias [6]. Granisetron is also a first generation 5-HT3 receptor antagonist but it is highly selective [7]. It acts specifically at 5-HT3 receptors on the vagal afferent nerves of the gut and produces irreversible block of the 5-HT3 receptors and this may account for the long duration of this drug [8,9].

Palonosetron is a second generation 5-HT3 receptor antagonist initially introduced and used for preventing chemotherapy induced nausea and vomiting. It has a greater binding affinity (>30 fold) and longer half-life. Recent receptor binding studies suggest that Palonosetron is further differentiated from other 5-HT3 receptor antagonists by interacting with 5-HT3 receptors in an allosteric, positively cooperative manner at sites different from those that bind with Ondansetron and Granisetron [10].

Because of its unique chemical structure, greater binding affinity with additional allosteric site and a substantially longer half-life of almost 40 hours made Palonosetron suitable for its use in prevention of PONV.

Hence we decided to carry out a comparative study of Palonosetron with Granisetron for prevention of PONV in female patients undergoing laparoscopic surgery.

Materials and Methods

After the institutional ethics committee approval and written informed consent, ninety six premenopausal female patients with ASA physical status I and II , aged ≥ 18years, scheduled to undergo elective gynaecological laparoscopic surgery under general anaesthesia were included in this study. We excluded Postmenopausal female patients, ASA class III and above, having obesity, history of allergy to study drugs and either pregnant or lactating mothers.

Sample size was calculated with reference to the study done by Dhurjoti Prosad Bhattacharjee et al. [11] and with the help of n-master software. We considered the type-1 (alpha) error as 0.05 and type-2 (beta) error as 0.2 and the sample size came to be forty eight in each group in our study.

Patients were explained in detail about the purpose and methodology of study. Patients were kept nil by mouth for minimum 6-8hours. Detailed preoperative assessment was performed on the previous day of surgery including history taking, general examination, systemic examination, airway assessment. All routine investigations were done like haemogram, blood sugar, blood urea, serum creatinine, liver function tests. X-ray chest and ECG were done when required. Patients were randomly divided with the help of random number generation software into two groups as follows:

Group P: Patients receiving Inj. Palonosetron 0.075mg IV (n=48 patients) and *Group G:* Patients receiving Inj. Granisetron 2.5mg IV (n=48 patients)

In the operation theatre multipara monitor was attached and baseline vital parameters were noted. Patients were Premedicated one minute before induction in the form of Inj. Glycopyrrolate 0.2 mg IV, Inj. Tramadol 1.0 mg/kg IV, Inj. Midazolam 0.01 mg/kg IV and Inj.Palonosetron O.O75mg IV (Group-P) or Inj Granisetron 2.5 mg IV (Group-G). After preoxygenation for 3 minutes with 100% oxygen, induction of anaesthesia was done by Inj. Thiopentone Sodium (2.5%) 4-7mg/kg IV till loss of eyelash reflex. Inj. Succinyl choline1.5-2mg/kg IV was given followed by tracheal intubation with appropriate size endotracheal tube. Appropriate size Ryle's tube was inserted and suction was done. Anaesthesia was maintained on closed circle system with controlled ventilation with O_2+N_2O (50%+50%), Inj. Vecuronium bromide 0.1mg/kg IV loading followed by top up of 0.025mg/kg IV and sevoflurane 2%.Ventilation was done to keep etCO2 between 35-45mm of Hg. Intra abdominal pressure was kept less than 14mm of Hg. Vital parameters like pulse, blood

pressure, SpO_2, $etCO_2$ were noted at every 15 minute interval till surgery lasted. Post operative analgesia in the form of Inj. Diclofenac sodium 75mg IM was given before reversal and then 12 hourly for 48 hour. At the end of surgery, residual neuromuscular block was adequately reversed with Inj. Glycopyrrolate 10mcg/kg IV and Inj. Neostigmine 50mcg/kg IV and after fulfilling criteria for the extubation, patients were extubated. Patients were transferred to post-anaesthesia care unit and kept there for 3 hours. After 3 hours, they were transferred to postoperative ward and here they were observed upto 48 hours. All episodes of PONV (complete response, nausea, retching, vomiting, emetic episode) were recorded for 0-3 hours in post-anaesthesia care unit and for 3-48 hours in postoperative ward.

Complete Response (free from emesis) was defined as no PONV and no need for any rescue medication.

Nausea was defined as unpleasant sensation associated with awareness of the urge to vomit.

Retching was defined as the laboured, spastic, rhythmic contraction of the respiratory muscles without the expulsion of gastric contents.

Vomiting was defined as the forceful expulsion of gastric contents from mouth.

Emetic episode was defined as retching plus vomiting episode.

Rescue antiemetic: Metoclopramide 10 mg IV was given as a rescue antiemetic when there were two or more episodes of PONV during first 48 hours.

Postoperative side effects in the form of headache, drowsiness and constipation were noted for 48 hours.

Results

All the parameters and variables studied were subjected to statistical analysis using Chi-square test and unpaired student 'T' test. As shown in Table 1, both the groups were comparable with respect to age, weight, ASA status and duration of surgery ($p>0.05$). Table 2 shows the incidence of nausea vomiting in postoperative period.

Complete Response

During 0-3 hours,the incidence of complete

Table 1: Demographic Data

Variable	Group-P Mean±SD	Group-G Mean±SD	Intergroup 'P' value
Age (year)	31.1042±8.0351	33.2083±7.9626	>0.05
Weight (kg)	53.1875±6.3066	51.9583±5.0737	>0.05
Duration of surgery (minutes)	77.1042±28.3250	70.3125±23.5969	>0.05
	ASA Grade (No. of patients)		
I	32	30	
II	16	18	

Table 2: Incidence of Post operative Nausea and Vomiting

Postoperative Period		Group-P		Group-G		'P' value
		No.	%	No.	%	
0-3 Hours	Complete response	34	70.83	39	81.25	0.33
	Nausea	10	20.83	5	10.41	0.26
	Retching	0	0	0	0	00
	Vomiting	4	8.33	4	8.33	0.71
	Emetic Episode	0	0	0	0	00
3-24 Hours	Complete response	25	52.08	18	37.5	0.21
	Nausea	17	35.41	19	39.58	0.83
	Retching	1	2.08	0	0	0.99
	Vomiting	5	10.41	6	12.5	0.99
	Emetic Episode	0	0	5	10.41	0.06
24-48 Hours	Complete Response	17	35.41	5	10.41	0.0076
	Nausea	16	33.33	12	25	0.5
	Retching	0	0	0	0	00
	Vomiting	14	29.16	28	58.33	0.0075
	Emetic Episode	3	6.25	8	16.66	0.2

response was 70.83% in Group-P; where as it was 81.25% in Group-G (p>0.05). During 3-24 hours, it was 52.08% in Group-P where as it was 37.5% in Group-G(p>0.05). During 24-48 hours, it was 35.41% in Group-P where as it was 10.41% in Group-G (p<0.01).

Nausea

During 0-3 hours,the incidence of nausea was 20.83% in Group-P;where as it was 10.41% in Group-G (p>0.05). During 3-24 hours, it was 35.41% in Group-P where as it was 39.58% in Group-G (p>0.05). During 24-48 hours, it was 33.33% in Group-P where as it was 25% in Group-G (p<0.01).

Vomiting

During 0-3 hours, the incidence of vomiting was 8.33% in both the groups (p>0.05). During 3-24 hours, it was 10.41% in Group-P where as it was 12.5% in Group-G (p>0.05). During 24-48 hours, it was 29.16% in Group-P where as it was 58.33% in Group-G (p<0.01).

Table 3 shows the number of patients who required rescue antiemetic medication. In our study we gave rescue antiemetic medication in the form of Inj. Metoclopramide 10mg IV when patient vomited for ≥ 2 times.

In Group-P, during 0-3hours; 2 patients required rescue antiemetic whereas during 3-24 hours, 1 patient required rescue antiemetic drug. During 24-48 hours, 10 patients required rescue drug. whereas in Group-G, during 0-3 hours; not a single patient required rescue antiemetic whereas during 3-24 hours, 2 patients required rescue antiemetic drug. During 24-48 hours, 18 patients required rescue drug.

Table 4 is showing the incidence of side effects in the form of headache, drowsiness and constipation in the postoperative period. Headache was observed in 1 patient in Group-P and 2 patients in Group-G during 0-3hours as well as 3-24 hours. Whereas during 24-48 hours 1 patient suffered headache in each group. No other side effects were observed in any of the two groups.

Discussion

PONV continues to be one of the most common complaints following surgery, occurring in more than 30% of patients or as high as 70% to 80% in certain high risk population without prophylaxis. Incidence of PONV after laparoscopic surgery is as high as 40%-75%. Stimulation of 5- HT3 receptors is the main cause in the initiation of vomiting reflex. These receptors are located peripherally on the nerve terminal of the vagus nerve and centrally on the chemoreceptor trigger zone (CTZ) of the area postrema and solitary tract nucleus (STN). Primarily anaesthetic agents induce vomitting by causing stimulation of the 5-HT3 receptors on the CTZ and also by releasing serotonin from the enterochromaffin cells of the small intestine.

We did not include a control group in our study; because it would be unethical if we don·t give any antiemetic drug to a patient undergoing laparoscopic surgery in which there are high

Table 3: Requirement of rescue medication

Time	No of patients who required rescue medication	
	Group-P	Group-G
0-3 hours	2	0
3-24 hours	1	2
24-48 hours	10	18

Table 4: Incidence of side effects

Side Effects	Time	Group-P(No.)	Group-G(No.)
Headache	0-3 hours	1	2
	3-24hours	1	2
	24-48hours	1	1
Drowsiness	0-3 hours	0	0
	3-24hours	0	0
	24-48hours	0	0
Constipation	0-3 hours	0	0
	3-24hours	0	0
	24-48hours	0	0

chances of PONV. *(Aspinall& Goodman)* [12]. The incidence of PONV after laparoscopic surgery is dependent on a variety of factors including age, sex, obesity, a history of previous PONV, surgical procedure, anaesthetic technique, and post operative pain [13]. The reasons for high incidence of PONV after laparoscopic surgery are not very clear. They may be related to the CO_2 gas that is used to create the pneumoperitoneum. Or else they may also be a side effect of the narcotic pain medications that are used perioperatively to control discomfort.

Complete Response

Murali prabhakar et al. [4] had given 40µg/kg of Inj. Granisetron and 0.075mg of Inj. Palonosetron i.v at the end of the surgery before extubation and concluded that there was significant difference in incidence of complete response between the two groups. patients receiving palonosetrone had overall complete response in 86.7% of cases whereas it was in 66.7% cases of Granisetrone group.

Kumkum Gupta et al. [15] and Bhattacharjee DP et al. [16] also observed in their study that incidence of complete response was 90% with palonosetrone whereas it was 86.6% with Granisetrone($p<0.05$) which is co relating with our study.

In our study, During 0-3 hours, the incidence of complete response was 70.83% in Group-P; where as it was 81.25% in Group-G ($p>0.05$). During 3-24 hours, it was 52.08% in Group-P where as it was 37.5% in Group-G ($p>0.05$). During 24-48 hours, it was 35.41% in Group-P where as it was 10.41% in Group-G ($p<0.01$). This states that palonosetrone is more effective in delayed PONV.

Mechanism of action of 5 HT3 receptor antagonists

5HT3 and NK-1 receptor antagonists are the mainstay of therapy especially to prevent CINV(cheomotherapy induced nausea vomiting). A number of studies have proven its use to prevent PONV also. *Granisetron* is a highly selective and potent first generation 5-HT3 receptor antagonist. It acts specifically at 5-HT3 receptors on the vagal afferent nerves of the gut. *Palonosetron* is a second generation 5-HT3 receptor antagonist. It binds to the serotonin binding site in addition to a second-or allosteric-site. Binding to an allosteric site causes a conformational change in the receptor that increases the overall affinity of the receptor for palonosetron and a much longer half-life, conferring a prolonged duration of action, exceeding 40 hrs, compared with other 5-HT3 receptor antagonists. In addition, palonosetron triggers *receptor internalization* resulting in a long-lived inhibition of receptor function. Accumulating evidence suggests that substance P (SP), that acts preferentially on neurokinin-1 (NK-1) receptors, not serotonin (5-HT), is the dominant mediator of delayed emesis. However, palonosetron does not bind to the NK-1 receptor (Wong et al., 1995) [17].But still many studies have proved its efficacy in delayed emesis. So, there is a concept of *" receptor cross-talk"*.

Receptor cross-talk, is defined as activation of one receptor by its ligand affecting cellular responses to another receptor system. Recent reports in the literature have shown that there is cross-talk between NK-1 and 5-HT3 receptor signaling pathways. For example, Hu et al. (2004) [18] explained that substance P (SP) which is an agonist at the NK-1 receptor, was shown to potentiate 5-HT3 receptor-mediated inward current in rat trigeminal ganglion neurons. In separate studies done by *Minami et al.(2001)* [19], 5-HT3 receptor antagonists were shown to block SP-mediated vagal afferent activation. Also NK-1 antagonism blocked serotonin-induced vagal afferent activation *(Minami et al., 2001)*[19]. These evidences of receptor signalling cross-talk raised the possibility that palonosetron's unique efficacy in delayed emesis could be caused by differential inhibition of the 5-HT3/NK-1 receptor cross-talk.

Rescue antiemetic drug was given when there were two or more episodes of PONV during first 48 hours. Regarding rescue treatment, all guidelines suggest that a drug should be used from a class that has not been given previously, especially when it is within the expected duration of action of the prior drug *(White PF, Watcha MF) [20]*. That is why we had selected Inj. metoclopramide 10mg IV as a rescue antiemetic drug. Our study results are co relating with that of *Murali Prabhakar et al. [14]*. We also required the need for rescue antiemetic more in Granisetrone group as compared to Palonosetrone group especially delayed post operative period(24-48 hours). In general, the frequently reported side effects for 5-HT3 receptor antagonists are Headache , dizziness and constipation [21].

Kovac et al 2008 [22] reported that adverse effects with a single therapeutic dose of granisetron and palonosetron were not clinically serious. Incidence of dizziness and constipation were not significant in their study but the incidence of headache was comparatively more in Group 'G'(16%) than in Group 'P' (10%). In the study conducted by *Bhattacharjee et al. [16]*, regarding the adverse effects like head ache, dizziness and drowsiness, granisetron group showed 10 % of patients with head ache and 13.3% of

patients with dizziness and for Palonosetron 10 % of patients with headache and 6.6 % with dizziness. These results are almost in agreement with our study.

So, this study concludes that the prophylactic single intravenous dose of palonosetron 0.075mg is more effective than granisetron 2.5mg for controlling postoperative nausea and vomiting between 24-48hours post operatively with less incidence of side effects.

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Conflicts of Interest: Non declared

Manuscript has been read and approved by all the authors. The requirements for authorship have been met and each author believes that the manuscript represents honest work.

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