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Comparison of the Efficacy of Palonosetron and Ondansetron in Prevention of Postoperative Nausea and Vomiting

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Abstract

Background and objectives: Post-operative nausea and vomiting (PONV) is commonly seen in female patients undergoing laparoscopic surgeries under general anaesthesia. Adverse consequences of PONV are patient dissatisfaction, unexpected hospital admission, and delayed recovery. In this randomized double blind prospective study, we compare the efficacy of ondansetron and palonosetron for prevention of PONV. *Material and methods:* After obtaining ethical clearance and informed consent, 130 female patients undergoing laparoscopic surgery were randomly divided into two groups by sealed envelope method. Group A 8mg ondansetron and group B received 8 mg ondansetron and 0.075 mg palonosetron iv respectively just before induction of general anaesthesia. During the postoperative period occurrence of nausea and vomiting, severity of nausea, rescue antiemetic use and adverse effects were monitored at 0-2 hrs, 2-6 hrs and 6-24 hrs. *Results:* Number of episodes of vomiting, risk for nausea and vomiting, severity of nausea and need for rescue medication was comparable between the 2 groups during the early post operative period (0- 2 hrs). During 2-6 hrs, the episode of vomiting and use of rescue antiemetic was not different between the two groups but severity of nausea and risk of nausea and vomiting was significantly lower in palonosetron group. During the late post operative period (6-24 hrs), the episodes of vomiting, risk for nausea and vomiting, severity of nausea and need for rescue antiemetics was significantly lower in palonosetron group. *Conclusion:* Intravenous palonosetron 0.075 mg has a better antiemetic profile when compared to ondansetron 8mg over 24hrs following laparoscopic surgeries under general anaesthesia.

Keywords: Laparoscopic surgery; anaesthesia; PONV; ondensetron; palanosetron.

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Introduction

Post operative nausea and vomiting (PONV) is a distressing side effect associated with general anaesthesia. Sir John Snow described the phenomenon of nausea and vomiting with chloroform anaesthesia [1]. The incidence of PONV was 75–80% when ether was used.

With the advent of modern and safer anaesthetic technique, incidence of PONV has decreased significantly. This is because ether is no longer used as anaesthetic, and use of prophylactic use of anti emetics in patients who are at risk of PONV.

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Aetiology of PONV is multi-factorial and several drugs have been used to treat this condition. At present the overall incidence ranges from 25-30% and intractable nausea and vomiting is seen in 0.18% of the patients under general anaesthesia.

PONV can lead to patient dissatisfaction, unexpected hospital admission for day care procedures, delayed recovery and return to work. It is difficult to ambulate patients with nausea and vomiting. Thus, PONV is one of the most undesirable post operative complications.

Causes of PONV are multi-factorial which include anaesthetic, surgical and patient factors. Apfel and his colleagues [2] have shown that it is possible to predict the individual patient's risk of PONV following balanced inhalational anaesthesia by considering a 4 factor risk score ; a) Female gender b) Non smoking status c) Previous h/o PONV and motion sickness d) Use of post operative opioids.

At present it is generally accepted that PONV can be controlled by blocking of all the receptors involved in vomiting. Various drugs have been used in the treatment of nausea and vomiting. 5-HT_3 receptor antagonist is one such antiemetic which has proven to be safe and effective in the treatment of PONV. 5-HT_3 receptor antagonists are also used in cancer chemotherapy. The drugs belonging to this group are Ondansetron, Granisetron, Ramosetron and Palonosetron, of which Ondensetron is most widely used. Palonosetron is a newly developed 5-HT_3 receptor antagonist. Its receptor-affinity is more potent than other antagonists. Its plasma half-life is very long ($t_{1/2}$ = 41 hrs). It is also known to be more effective than ondansetron against nausea and vomiting in patients using anticancer drugs. However, studies comparing the effects of preventing PONV between palonosetron and other 5-HT3 receptor antagonists are sparse.

The present randomized double blind study is designed to evaluate the efficacy of palonosetron compared with ondansetron for preventing PONV in female patients undergoing laparoscopic surgeries.

Materials and methods

After obtaining the approval from the institutional ethical committee, this prospective, randomized, comparative study was undertaken comparing the effects of ondansetron and palonosetron in preventing PONV in female patients undergoing laparoscopic surgeries.

Female patients belonging to American Society of Anaesthesiology Physical Status (ASA PS) I and II, aged between 18 and 60 years, undergoing elective laparoscopic surgery under general anaesthesia with endotracheal intubation were enrolled for the study. Patients who had received anti emetics, steroids or psychoactive medications within 24 hrs of the study initiation or received cancer chemotherapy within 4 weeks or emetogenic radiotherapy within 8 weeks before the study entry, pregnant or lactating patients and patients with vomiting or retching in the 24 hours preceding the surgery were not included in the study.

Based on study by S K park et al. [3], it was calculated that a sample size of 61 per group was required to compare PONV between the two groups with 5% level of significance and 80% power. We allocated 65 patients to each group in our study

Preoperative assessment: Preoperative evaluation of all the patients was performed including detailed history regarding motion sickness and PONV in the past. All the patients were kept nil per oral for 8 hours and were premedicated with Tab pantoprazole 40 mg and Tab alprazolam 0.5 mg on the night before the surgery.

Induction and maintenance: Patient were randomly allocated into either Group A (ondansetron) or group B (palonosetron) by sealed envelope method. In all selected patients baseline vital parameters were noted. In subjects of group A - ondansetron 8 mg as a bolus iv dose and in group B-palonosetron 0.075 mg diluted up to 4 ml with distilled water was administered before induction of anaesthesia. The person administering the study drug and assessing post operatively was different and both were blinded to study drug.

Anaesthesia was induced with intravenous (iv) Fentanyl 2 mcg/kg and Propofol 2 mg/kg and tracheal intubation facilitated with atracurium 0.5 mg/kg. Anaesthesia was maintained with N_2O in oxygen 60 : 40% mixture and a 1 - 1.5 mac of isoflurane. At the completion of surgery patients received Neostigmine 0.05 mg/kg and Glycopyrollate 0.008 mg/kg for reversal of neuro-muscular blockade.

Post operative monitoring: The occurrence of nausea and vomiting, severity of nausea according to verbal descriptive scale (VDS) (0 = no nausea, 1 = mild nausea, 2 = moderate nausea, 3 = severe nausea) and rescue antiemetic drug use was monitored at 0-2 hrs, 2-6 hrs and 6-24 hrs after surgery.

Nausea was defined as a subjective unpleasant sensation associated with awareness of urge to vomit. Vomiting was defined as forceful expulsion of gastric contents from the mouth. Retching was defined as laboured, rhythmic, spasmodic contractions of respiratory muscles without expulsion of gastric contents. Metoclopramide 10 mg iv was used as a rescue antiemetic when 2 episodes of vomiting had occurred or VDS more than 2 or if the patient requested for it. A detail of any adverse effects was recorded.

Data was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square was used as test of significance. Continuous data was represented as mean and standard deviation. ANOVA test was the test of significance for mean difference between more than two groups. Paired t test was the test of significance for paired data (baseline versus at different interval comparison). p value <0.05 was considered as statistically significant. Poisson regression was used to compare the number of episodes of vomiting over time between the study groups. Generalized estimating equation was done to assess the effect of intervention on the presence of nausea or vomiting over time.

Results

The study was conducted on 130 female patients. Laparoscopic surgery was converted to open surgery in two patients who received palonosetron, and hence, they were excluded from the study. Patient characteristics such as age, ASA status, baseline vital parameters, weight and history of motion sickness or previous history of PONV and surgical factors like duration of anaesthesia and surgery were comparable between the two groups (Table 1).

The number of episodes of vomiting, risk for nausea and vomiting with respect to duration for intervention, severity of nausea and need for rescue medication was comparable between the 2 groups during 0- 2 hrs.

Table 1: Demographic details

Variables		Ondansetron (n=65)	Palonosetron (n=65)	p value
Age (years)		41.95 ± 12.21	38.52 ± 12.46	0.118
Blood pressure (mmHg)	systolic	136.65 ± 15.422	13.6 ± 16.193	0.818
	diastolic	82.02 ± 8.005	81.62 ± 8.713	0.789
SPO2 (%)		98.57 ± 1.015	98.59 ± 0.90	0.916
ASA PS	1	36(55.4%)	35(55.6%)	0.984
	2	29(44.6%)	28(4.4%)	
Body weight (kgs)		63.09 ± 7.875	61.90 ± 7.237	0.376
Motion sickness history	No	84.6%	82.5%	0.751
	Yes	15.4%	17.5%	
PONV in past	No	83.1%	82.5%	0.936
	Yes	16.9%	17.5%	
Duration (mins)	Surgery	102.54 ± 46.02	110.95 ± 49.79	0.323
	Anaesthesia	137 ± 50.996	145.95 ± 49.98	0.318

Table 2: Comparison of episodes of vomiting, severity of nausea vomiting according to VDS, use of rescue anti emetics and adverse effects between ondansetron and palonosetron at 0-2, 2-6 and 6-24 hrs

			Groups			P Value
			Ondensetron	Palonosetron	Total	0.05
0-2 hours	Episodes of vomiting	1 Episode	5	0	5	
		2 Episodes	0	1	1	
		No	60	62	122	
	Severity of nausea (VDS)	0	45	51	96	0.378
		1	14	8	22	
		2	5	4	9	
		3	1	0	1	
	Use of rescue antiemetics	No	59	60	119	0.323
		Yes	6	3	9	
	Adverse effects	Headache	0	2	2	0.148
		Absent	65	61	126	

2-6 hours	Episodes of vomiting	1 Episode	10	3	13	0.05
		2 Episodes	0	1	1	
		No	55	59	114	
	Severity of nausea (VDS)	0	26	47	73	<0.001
		1	26	11	37	
		2	5	2	7	
		3	8	3	11	
	Use of rescue antiemetics	No	54	58	112	0.181
		Yes	11	5	16	
	Adverse effects	Headache	3	6	9	0.210
		Headache + lightheadedness	0	1	1	
		Headache + dizziness	0	2	2	
		Absent	62	54	116	
6-24 hours	Episodes of vomiting	1 Episode	12	5	17	0.060
		2 Episodes	6	2	8	
		No	47	56	103	
	Severity of nausea (VDS)	0	20	41	61	<0.001
		1	27	16	43	
		2	12	5	17	
		3	6	1	7	
	Use of rescue antiemetics	No	45	57	102	0.003
		Yes	20	6	26	
	Adverse effects	Headache	4	12	16	0.027
		Absent	61	51	112	

During 2-6 hrs, severity of nausea and risk of nausea and vomiting was significantly lower in palonosetron group.

During 6-24 hrs, the episodes of vomiting, risk for nausea and vomiting, severity of nausea and need for rescue antiemetics was significantly lower in palonosetron group.

The side effect profile was comparable between the two groups in 0-2 and 2-6 hrs postoperatively but was significantly higher in palonosetron group during 6-24 hrs of post operative period (Table 2).

Table 3: Poisson Regression analysis: To find the relationship between type of intervention and number of episodes with respect to duration of intervention.

Time	Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test			Exp (B)	95% Wald Confidence Interval for Exp (B)	
				Lower	Upper	Wald Chi-Square	df	Sig.		Lower	Upper
	(Intercept)	-3.450	0.7071	-4.836	-2.064	23.805	1	0.000	0.032	0.008	0.127
0-2 hrs	Ondansetron Group	.662	0.8660	-1.035	2.359	0.584	1	0.445	1.938	0.355	10.583
	Palonosetron Group	0[a]	.	.	.	.	.	.	1	.	.
	(Intercept)	-2.534	0.4472	-3.410	-1.657	32.098	1	0.000	0.079	0.033	0.191
2-6 hrs	Ondansetron Group	0.662	0.5477	-0.412	1.735	1.460	1	0.227	1.938	0.663	5.671
	Palonosetron Group	0[a]	.	.	.	.	.	.	1	.	.
	(Intercept)	-1.946	0.3333	-2.599	-1.293	34.079	1	0.000	0.143	0.074	0.275
6-24 hrs	Ondansetron Group	0.950	0.3909	0.183	1.716	5.902	1	0.015*	2.585	1.201	5.560
	Palonosetron Group	0[a]	.	.	.	.	.	.	1	.	.

Table 4: Generalized estimating equation: To assess the effect of intervention on the presence of nausea or vomiting over time – Linear regression model

Parameter Estimates											
Time	**Parameter**	**B**	**Std. Error**	**95% Wald Confidence Interval**		**Hypothesis Test**			**Exp(B)**	**95% Wald Confidence Interval for Exp(B)**	
				Lower	**Upper**	**Wald Chi-Square**	**df**	**Sig.**		**Lower**	**Upper**
0-2 hrs	(Intercept)	0.190	0.192	-0.186	0.567	0.981	1	0.322	1.210	0.830	1.764
	Ondansetron Group	0.117	0.075	-0.031	0.265	2.401	1	0.121	1.124	0.969	1.304
	Palonosetron Group	0a	.	.	.	.	.	.	1	.	.
2-6 hrs	(Intercept)	0.254	0.233	-0.204	0.712	1.179	1	0.277	1.289	0.815	2.039
	Ondansetron Group	0.346	0.060	0.227	0.465	32.573	1	<0.0001*	1.413	1.255	1.592
	Palonosetron Group	0a	.	.		.	.	.	1	.	.
6-24 hrs	(Intercept)	0.349	0.285	-0.211	0.910	1.492	1	0.222	1.418	.810	2.483
	Ondansetron Group	0.343	0.044	0.256	0.430	60.058	1	<0.0001*	1.409	1.292	1.537
	Palonosetron Group	0a	.	.	.	.	.	.	1	.	.

Discussion

PONV continues to be an undesirable problem postoperatively, in spite of significant advances in general anaesthesia care. It results in significant patient distress and potentially affects post operative recovery, may result in delayed discharge from hospital and/or readmission. Morbidity associated with PONV includes dehydration, electrolyte imbalance, aspiration and surgical complications like bleeding and wound dehiscence.

Female gender, non-smoker status, history of PONV or motion sickness, use of perioperative opioids, use of volatile anaesthetics, duration of surgery, duration of anaesthesia, and type of surgery are all risk factors for PONV. In this study, these risk factors were similar in the two groups. Therefore, the difference in PONV incidence between the groups can be attributed to the study drug.

The newest class of antiemetics used for the prevention and treatment of PONV are the serotonin receptor antagonists (Ondansetron, Granisetron, Dolasetron, Palonosetron).

Ondansetron is a potent, highly selective 5-HT_3 receptor antagonist. The mechanisms of action of Ondansetron are both central and peripheral. It blocks the 5-HT_3 in the area postrema, nucleus tractus solitarius (NTS) and adjacent areas in the brain, which are related to nausea and vomiting. Also, it blocks 5-HT_3 receptors in the mucosal vagal afferents in the gastrointestinal tract.

Palonosetron is a "second generation" 5-HT_3 receptor binding agent newly approved by FDA for the prevention of PONV since March 2008. It has the highest binding affinity to the 5-HT_3 receptor and at approximately 40 hours, has the longest elimination half life. Unlike the representatives of the first generation with competitive inhibition of the 5-HT_3 receptor, Palonosetron seems to exhibit allosteric binding leading to effects persisting beyond the mere receptor binding time.

Paventi et al. [4] compared the efficacy of 4 mg versus 8 mg ondansetron for the prevention of PONV after laparoscopic cholecystectomy and concluded that 8 mg was more effective than 4 mg. A study by Candiotti and colleagues [5] comparing three different doses of palonosetron with placebo in elective laparoscopic abdominal and gynaecological surgery, a single 0.075 mg i.v. dose of palonosetron significantly increased the complete response rate (no emetic episodes and no rescue medication) compared with placebo during the 0–24 hr postoperative period, but not during the 24–72 hr postoperative interval. The doses of drugs used in the present study were based on the optimal dose for prophylaxis of PONV in these studies; thus, 0.075 mg palonosetron and 8 mg ondansetron were chosen. We did not include a control group receiving placebo in our study,

since placebo controlled trials may be considered unethical in view of the distressing implications of PONV.

It has been reported that patients receiving general anaesthesia with volatile agents, nitrous oxide and opioids were 11 times more likely to experience PONV than in other forms. In our study as our purpose was to compare the efficacy of two drugs under similar surgical and anaesthetic 0conditions, we did not avoid any of these agents.

In this study, 92.3% patients who received ondansetron didn't have any vomiting in the first 2 hrs postoperatively compared to 98.4% patients who received palonosetron. 84.6% patients and 72.3% patients in ondansetron group didn't have vomiting between 2-6 hrs and 6-24 hr period respectively compared to 93.7% and 88.9% in palonosetron group. This was statistically insignificant (p= 0.05 for 0-2 hrs, p = 0.087 for 2-6 hrs, p = 0.060 for 6-24 hrs).

In a study done by B. Laha et al. [6] comparing efficacy of ondansetron and palonosetron in preventing PONV following laparoscopic cholecystectomy, the incidence of vomiting between the two groups was also found to be statistically insignificant (p = 0.262 for 0-2 hrs, p = 0.176 for 2-6 hrs, p = 0.523 for 6-24 hrs). This was comparable to the results of our study.

Y.E. Moon et al. [7] in a study comparing ondansetron with palonosetron in prevention of PONV following thyroidectomy, used VDS to assess the severity of nausea and found it to be statistically insignificant in the first 2 hrs but significantly less in palonosetron group than ondansetron group during 2-24 hrs (p = 0.03). In our study, severity of nausea as assessed by VDS was found to be statistically insignificant between the two groups during the first 2 hours. However during the 2-6 hrs time period and 6-24 hr period, the severity of nausea was significantly higher in ondansetron group compared to palonosetron group (p = 0.001{2-6 hrs}, p<0.001 {6-24 hrs}) This was comparable to study by Y. E Moon et al.

In studies done by Taninder Singh et al. [8] and Nupur Chakravarthy et al. [9], the incidence of nausea was found to be significantly lower in palonosetron group compared to ondansetron group (p = 0.037 and p = 0.026 respectively). However the severity of nausea at different time intervals was not assessed in these studies.

Poisson's regression was used to find the relation between the type of intervention and number of episodes of vomiting with respect to duration of intervention and we found statistically significant higher risk of vomiting in ondansetron group compared to palonosetron group during 6-24 hrs post operatively (p = 0.015). This showed that with increase in duration of intervention, the number of episodes of vomiting was significantly higher in ondansetron group than palonosetron group.

Generalised estimating equation was used to assess the effect of intervention on the presence of nausea and vomiting over time and it showed that there was no significant difference in the risk of nausea and vomiting between the two groups during the first 2 hrs (p= 0.125). However, there was statistically significant higher risk for vomiting and nausea in the ondansetron group compared to the palonosetron group in 2-6 hrs and 6-24 hrs (p < 0.001).

Thus in our study, the number of episodes of vomiting, the severity of nausea and the risk for vomiting and nausea over time was significantly higher in ondansetron group than palonosetron group.

It has been recommended that in cases of breakthrough PONV, repeat antiemetic should be of a different class than the one used for prophylaxis. Metoclopramide was used as a rescue antiemetic for this very reason. In our study, there was no difference in the use of rescue antiemetics between the two groups in the first 6 hours post operatively. However from 6 to 24 hrs period, the use of rescue antiemetic was significantly higher in those who received ondansetron than those who received palonosetron (p = 0.003).

Sukhminderjit Singh Bajwa, et al. [10] in a prospective double blind study comparing the efficacy of 8 mg of Ondansetron with Palonosetron 0.075 mg iv in preventing PONV and also found similar results. This suggests that palonosetron has an antiemetic effect which lasts longer than ondansetron. The exact reason for the difference in effectiveness between the two drugs is believed to be related to the half lives (ondansetron 3-5 hrs versus palonosetron 40 hrs) and/or the binding affinities of 5-HT_3 receptor antagonists. Both the manner as well as the site of binding of palonosetron with 5-HT_3 receptors is different from that of ondansetron. The nature of this receptor binding may modify the functional responses to serotonin thus affecting the efficacy of drug.

The comparable PONV characteristics in both groups in the early post operative phase, followed by a significant difference in response in the later recovery period serve to accentuate the efficacy of palonosetron in long term prophylaxis.

The 5-HT_3 antagonists are safe with mild and transient side effects (e.g. headache, constipation, dizziness).

S K Park et al [3], in their study found comparable side effect profiles between palonosetron and ondansetron when used for prevention of PONV. However in our study, we found the incidence of sides effects namely headache and dizziness to be higher in palonosetron group compared to ondansetron at all time periods.

Conclusion

0.075 mg of palonosetron when administered before induction of general anaesthesia, the severity of nausea and risk for nausea and vomiting was significantly less compared to 8mg of ondansetron during 2 -6 hrs of post operative period.

The number of episodes of vomiting with respect to duration of intervention, severity of nausea and risk of nausea and vomiting was significantly lower in palonosetron group compared to ondansetron group during 6-24 hrs of post operative period.

The use of rescue antiemetics was also found to be significantly less in the palonosetron group compared to ondansetron group in 6-24 hrs of post operative period.

The side effects namely headache and dizziness was higher in palonosetron group than ondansetron group.

Thus we conclude that palonosetron is more effective antiemetic as compared to ondansetron for prevention of PONV in female patients undergoing laparoscopic surgeries under general anaesthesia.

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