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A COMPARATIVE STUDY OF GRANISETRON AND PALONOSETRON FOR PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING FOLLOWING LAPAROSCOPIC SURGERY.

KEYWORDS: GRANISETRON,PALONOSETRON, NAUSEA,VOMITING,5-HT3 receptors LAPAROSCOPIC SURGERY

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ABSTRACT *Context: Granisetron and Palonosetron for prevention of postoperative Nausea and Vomiting fol-lowing laparoscopic surgery.*

AIM: aim of our study was to Comparison Granisetron and Palonosetron for prevention of post-operative Nausea and Vomiting following laparoscopic surgery.

Settings and Design: Sixty adults patients of class ASA I and II of either sex in age

group between 20 to 70yrs, scheduled for elective laparoscopic surgeries were se

lected for the study. Patients were randomly divided into two groups 30 each.

Group 'G' : Granisetron group

Group 'P' : Palonosetron group

Materials and Methods: At the end of the surgery before extubation Group G patients re-ceived 40µg/kg of Inj. Granisetron and Group P patients received 0.075mg of Inj. Palonosetron slowly i.v over a period of 30 seconds

Statistical Analysis Used: Comparibility of groups are analyzed by ANOVA followed by un paired 't' test Chi-square test, fisher exact test.there was no significant difference between the two groups.($p > 0.05$).

Results: The incidence of nausea was significantly more with patients who received granisetron than when compared with patients who received palonosetron during delayed PONV period (12 – 48 hrs).No statistically significant difference is present between palonosetron group and grani-setron group for the prevention of vomiting both during early and delayed PONV period.

Conclusion: We have observed that:Nausea and vomiting is more common in female patients undergoing Laparoscopic surgery.Over all complete response occurred in granisetron was 66.7% and Palonosetron group was 86.7%. Palonosetron is more effective than Granisetron in prevent-ing PONV upto 48 hrs (even upto 72 hrs in the study conducted by other authors).Palonosetron has less incidence of side effects as compared to granisetron.Use of rescue antiemetic is less with the Palonosetron as compared to granisetron.Palonosetron is more potent and long acting as compared to granisetron.

INTRODUCTION

Over the past several decades, as the risk of major mortality due to surgery has decreased, attention has been shifted to addressing factors that negatively influence patient morbidity and patient satisfaction, such as postoperative nausea and vomiting (PONV).

PONV continues to be one of the most common symptoms occuring after surgery , occuring in more than 30% of surgeries[1] or as high 70% to 80% in certain high risk population without prophylaxis[2] prolonging the patient stay in the post operative care unit, therefore increasing the hospital expenses.

PONV though generally non fatal and self limiting, may lead to rare but serious medical consequences, including dehydration and electrolyte imbalance, disruption of surgical repair and increase the perception of pain[3].

The aetiology of post operative nausea and vomiting is complex and depends on variety of factors, including patient characteristics, type of surgery, anaesthetic technique and post operative care . PONV is more common in female patients. Women undergoing laparoscopic surgeries are particularly at risk of experiencing these problems[4] because of female hormones.

A number of pharmacological agents (antihistamines, prokinetics, phenothiazines, butyrophenones, dopamine receptor antagonists) have been tried for the prevention and treatment of PONV but undesirable adverse effects such as excessive sedation, hypertension, dry mouth, dysphoria, hallucination, and extrapyramidal symptoms have been noted[5]

5 hydroxytryptaminetype3 ($5HT_3$) receptor antagonists are devoid of such side effects and highly effective in prevention and treatment of PONV.

Granisetron is a highly selective and potent 5-HT_3 receptor antagonist[6]. It acts specifically at 5-HT_3 receptors on the vagal afferent nerves of the gut. Granisetron produces irreversible block of the 5-HT_3 receptors and it may account for the long duration of this drug[7.8].

Palonosetron is a 5-HT_3 receptor antagonist initially introduced and used for preventing chemotherapy induced nausea and vomiting. This unique 5-HT_3 receptor antago-

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nist has a greater binding affinity and longer half-life than older 5-HT_3 antagonists like ondansetron. Recent receptor binding studies suggest that palonosetron is further differentiated from other 5-HT_3 by interacting with 5-HT_3 receptors in an allosteric, positively cooperative manner at sites different from those that bind with ondansetron and granisetron[9]. In addition, this sort of receptor interaction may be associated with long lasting effects on receptor ligand binding and functional responses to serotonin[10].

MATERIAL AND METHODS

STUDY DESIGN:

This was a prospective, randomized, single blinded, comparative study conducted at Kurnool Govt.General Hospital,Kurnool District.Andhra Pradesh,India.

This study was approved by ethical committee of our institution.

All the patients were well informed about study and informed written consent was taken from patients in both groups.

STUDY POPULATION:

Sixty adults patients of class ASA I and II of either sex in age group between 20 to 70yrs, scheduled for elective laparoscopic surgeries were selected for the study.

Patients were randomly divided into two groups 30 each.

Group 'G' : Granisetron group (n =30), 40µg/kg.

Group 'P' : Palonosetron group (n = 30), 0.075mg.

INCLUSION CRITERIA :

- ASA physical class I and II.
- Age between 20 to 70 yrs.
- Elective laparoscopic gynaecological and abdominal surgeries.
- Surgery for which the duration is expected to last for atleast 30 minutes or more.

EXCLUSION CRITERIA :

- ASA physical class III and above .
- Inability to understand or co-operative with the study.
- Hypersensitivity to drugs.
- Extremes of age.
- Emergency surgeries.
- Patients suffering from motion sickness, severe pulmonary,
- Gastrointestinal (GERD), cardiovascular, renal, hepatic, endocrinological diseases and neurological diseases.
- Patients who received antiemetics 24hrs prior to surgery or had emetic episode 24 hrs prior to the study.
- Pregnant and lactating female patients.

PREOPERATIVE ASSESSMENT :

A complete preoperative evaluation of patient was done with history, physical examination, relevant investigations. ASA physical classification was done on the basis of preanaesthetic evaluation. Patients enrolled in the study as per inclusion and exclusion criteria.

Patient were kept NPO for 10 hrs before surgery.

In the preoperative room, iv line was secured. In the operation theatre routine monitoring devices pulse oximetry, NIBP, ECG monitors were attached, and baseline blood pressure, heart rate and 02 saturation values were recorded. The anaesthetic regimen and surgical procedures were standardised for all patients. Patient premedicated with I.V Inj. Glycopyrrolate 0.2mg/kg and I.V Inj. fentanyl 1.5µg/kg. Induction was done by sleep dose of Inj. Thiopentone I.V, after confirming ventilation, tracheal intubation was facilitated by I.V inj. suxamethonium 1.5mg/kg. Anaesthesia was maintained with N_20 66% , 02 33%, halothane 0.5 - 2% and intermittent doses of vecuronium bromide and fentanyl was used as per surgical requirement

Ventilation was maintained mechanically and adjusted so as to keep the end tidal carbondioxide 35 - 40mm of Hg. During surgery the patients were placed in trendlenberg position and right up position and the abdomen was insufflated with carbondioxide with an intra abdominal pressure of 12 -15 mm of Hg. Patients were monitored intraoperatively by continuous ECG, blood pressure, Spo_2, $Etco_2$ and hourly urine output measurement.

At the end of the surgery before extubation Group G patients received 40µg/kg of Inj.Granisetron and Group P patients received 0.075mg of Inj. Palonosetron slowly i.v over a period of 30 seconds. After completion of surgery, patient was made supine and residual pneumoperitoneum removed, stomach emptied with nasogastric tube suction. After return of respiratory attempts, residual neuromuscular block was antagonized with Inj. glycopyrrolate 0.4mg and Inj. neostigmine 0.05mg/kg and extubated after patient became awake and with adequate tone, power, reflexes.

In post anaesthesia care unit blood pressure and heart rate was recorded every 10 minutes for 30minutes. Episodes of nausea and vomiting experienced by each patient was recorded by direct questioning the patient and nursing staff. The number of patients who suffered from nausea or vomiting and number of times vomited was noted during the periods of 0-4hrs, 4-12hrs, 12-24hrs, 24-48hrs.

Assessment of PONV:

The terms nausea, retching and vomiting were defined as follows

- Nausea is defined as unpleasant feeling of urge to vomit.
- Retching is defined as labored, rhythmic, spasmodic, contractions of respiratory muscles without forceful expulsion of gastric contents from mouth.
- Vomiting is defined as labored, rhythmic, spasmodic, contractions of respiratory muscles with forceful expulsion of gastric contents from mouth.

Rescue medication was given to all patients who had uncontrolled nausea and vomiting inspite of the study drugs given. Rescue medication in the form of Inj. metoclopramide 10mg was given intravenously.

Study medication was assessed in terms of,

- Incidence of PONV (nausea, nausea requiring rescue medication, vomiting).
- Percentage of patients requiring rescue antiemetic.
- Number of times rescue given.
- Number of patients with complete re sponse.
- Details of any side effects like head ache, dizziness, constipation were also ob served.

The results were tabulated and analyzed by statistical analysis, Chi-squar test, fisher exact test, student 't' test.

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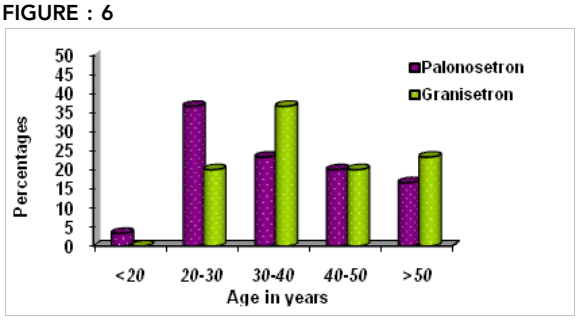
RESULTS:

Table 1 : Age distribution

Age in years	Palonosetron		Granisetron	
	No	%	No	%
<20	1	3.33	0	0.0
20-30	11	36.6	6	20.0
30-40	7	23.3	11	36.6
40-50	6	20.0	6	20.0
>50	5	16.6	7	23.3
Total	30	100.0	30	100.0
Mean ± SD	35.90±11.43		39.77±10.89	

Samples are age matched with p = 0.185

FIGURE : 6



The above table shows age distribution between palonosetron group and granisetron group.

The age range was between 20 - 60 yrs.

The mean values of age with standard deviation was

Palonosetron group 35 . 90 ± 11.43.

Granisetron group 39. 77 ± 10.89.

There was no significant difference between the two groups (p > 0.05).

Table 2 : Gender distribution

Gender	Palonosetron		Granisetron	
	No	%	No	%
Male	11	36.6	11	36.6
Female	19	63.4	19	63.4
Total	30	100.0	30	100.0

Samples are gender matched with P =0.605

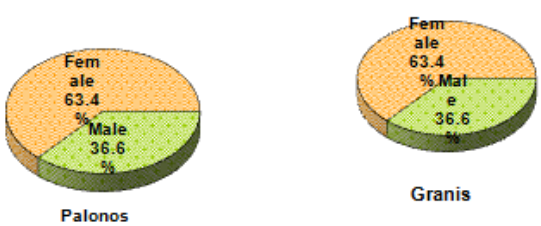


FIGURE : 7

In our study , female predominated the males in both palonosetron group and granisetron group (i.e females 63.4% and males 36.6%), it was just a coincidence.

No significant difference was observed in sex distribution between both the groups.

Table 3: Weight (kg) distribution

Weight (kg)	Palonosetron		Granisetron	
	No	%	No	%
36-40	0	0.0	2	6.6
40-50	8	26.6	2	6.6
50-60	9	30.0	13	43.4
>60	13	43.4	13	43.4
Total	30	100.0	30	100.0
Mean ± SD	57.23±8.17		56.57±9.17	

Samples are weight matched with P = 0.767

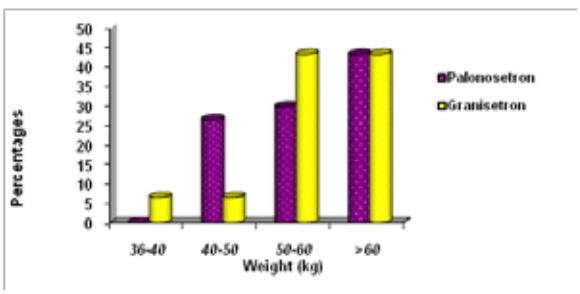


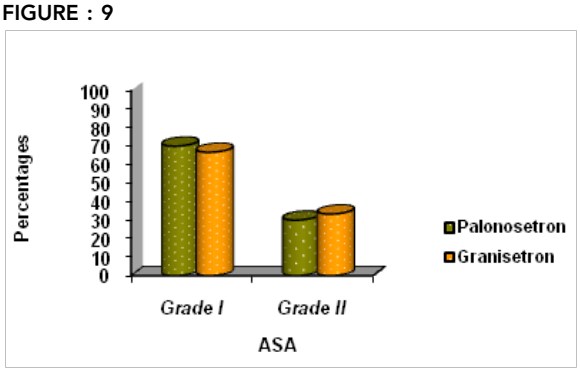
FIGURE : 8

- Mean values of weight with standard deviation was
- Palonosetron group = 57.23 ± 8.17.
- Granisetron group = 56.57 ± 9.17.
- No significant difference was observed in weight between both the groups.

Table 4: ASA grade

ASA	Palonosetron		Granisetron	
	No	%	No	%
Grade I	21	70.0	20	66.7
Grade II	9	30.0	10	33.3
Total	30	100.0	30	100.0

FIGURE : 9



In palonosetron group 70% patients were ASA grade I and 30% were ASA grade II.

In granisetron group 66.7 % patients were ASA grade I and 33.3 % were ASA grade II.

Distribution of ASA grade is statistically similar in two groups (P=0.500).

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Table 5: TYPES OF SURGERY.

Procedure	Palonosetron		Granisetron	
	No	%	No	%
LAC	10	33.3	15	50.0
DHL	2	6.7	4	13.3
LTO	4	13.3	2	6.7
LA	1	3.3	3	10.0
LH	2	6.7	2	6.7
LOC	0	0.0	3	10.0
Others	11	36.7	1	3.3
Total	30	100.0	30	100.0

LAC : Laparoscopic assisted cholecystectomy.
DHL : Diagnostic hysterolaparoscopy.
LTO : Laparoscopic tubal ligation.
LA : Laparoscopic appendicectomy.
LH : Laparoscopic assisted hernia repair.
LOC : Laparoscopic ovarian cystectomy.
Others : Laparoscopic varicolocele, laparoscopic assisted vaginal Hysterectomy.

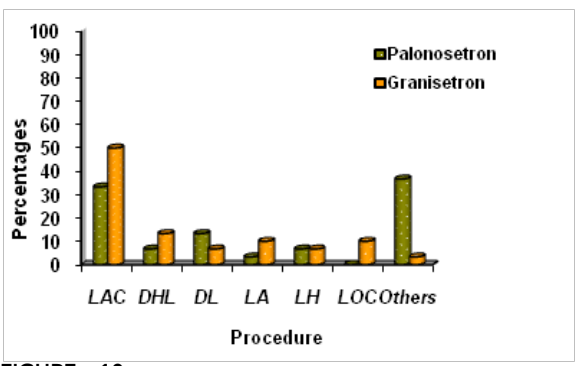


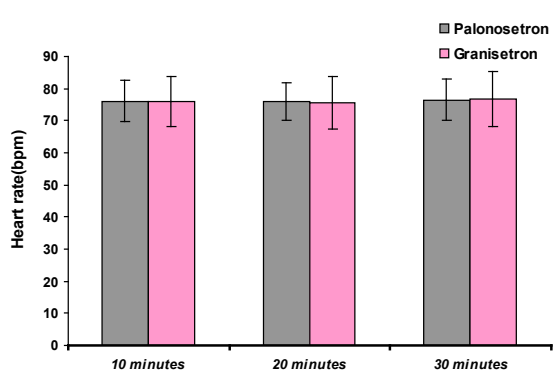
FIGURE : 10
Above types of procedures were included in our study.

Laparoscopic assisted cholecystectomy procedure predominated than other procedures in both the groups.

Table 6: Comparison of Heart rate (bpm)

Heart rate(bpm)	Palonosetron	Granisetron	P value
10 minutes	76.03±6.42	76.00±7.93	0.986
20 minutes	76.16±5.84	75.53±8.19	0.732
30 minutes	76.50±6.49	76.63±8.59	0.946

FIGURE :11

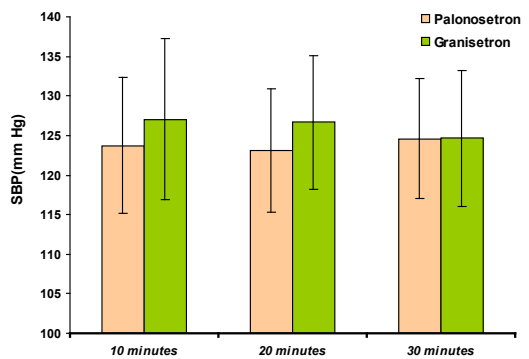


INFERENCE :Shows no statically significant difference in heart rate post operatively in PACU between both the groups.

Table 7: Comparison of SBP

SBP(mm Hg)	Palonosetron	Granisetron	P value
10 minutes	123.73±8.56	127.06±10.22	0.176
20 minutes	123.13±7.78	126.67±8.44	0.097
30 minutes	124.60±7.57	124.66±8.60	0.975

FIGURE : 12

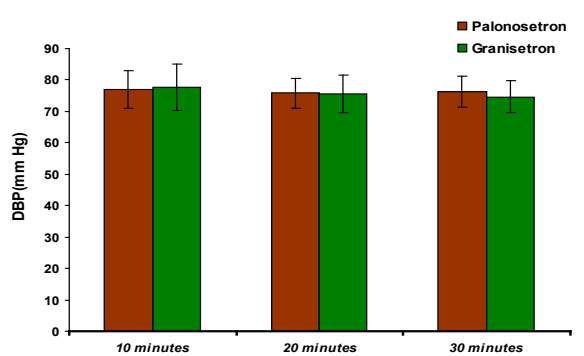


INFERENCE :
Shows no statically significant difference in SBP post operatively in PACU between both the groups.

Table 8: Comparison of DBP

DBP(mm Hg)	Palonosetron	Granisetron	P value
10 minutes	77.00±6.00	77.80±7.37	0.647
20 minutes	75.83±4.78	75.73±5.95	0.943
30 minutes	76.26±4.94	74.67±5.10	0.222

FIGURE : 13



INFERENCE :
Shows no statically significant difference in DBP postoperatively in PACU between both the groups.

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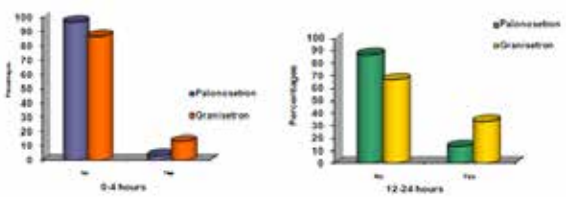
Table 9: Incidence of Nausea in two groups

Nausea	Palonosetron (n=30)		Granisetron (n=30)		P value
	No	%	No	%	
0-4 hours					
No	29	96.7	26	86.7	0.112
Yes	1	3.3	4	13.3	
4-12 hours					
No	27	90.0	24	80.0	0.472
Yes	3	10.0	6	20.0	
12-24 hours					
No	26	86.7	20	66.7	0.063+
Yes	4	13.3	10	30.0	
24-48 hours					
No	27	90.0	21	70.0	0.052+
Yes	3	10.0	9	33.3	

FIGURE : 14



Above table and graph shows the following results :
In early hours (0 - 4hrs) 1 patient (3.3%) in palonosetron group had nausea while 4 patients (13. 3%) in granisetron group had nausea. The incidence of nausea was not statically significant between both groups(p > 0.05).

Between 4 - 12 hrs, 3 patients (10%) had nausea in palonosetron group and 6 patients (20%) had nausea in granisetron group. The incidence of nausea was not statically significant between both groups(p > 0.05).

Between 12 – 24 hrs , 4 patients(13.3%) in palonosetron group and 10 patients (30.0%) in granisetron had nausea showing statically no significant (p = 0.067) though clinically significance is present.

Between 24 – 48 hrs , 3 patients (10 %) in palonosetron group and 9 patients(33.3 %) in granisetron group had nausea showing both statical (p = 0.052) and clinical significance .

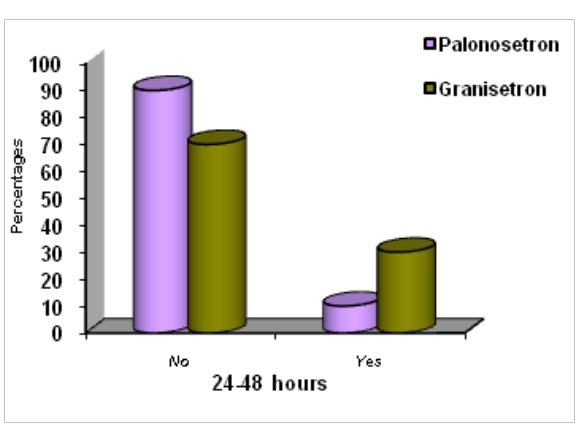
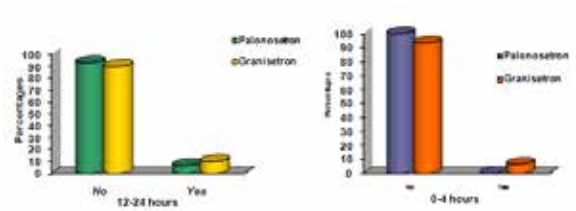


Table 10: Incidence of Vomiting

Vomiting	Palonosetron (n=30)		Granisetron (n=30)		P value
	No	%	No	%	
0-4 hours					
No	30	100.0	28	93.3	0.492
Yes	0	0.0	2	6.7	
4-12 hours					
No	28	93.3	28	93.3	1.000
Yes	2	6.7	2	6.7	
12-24 hours					
No	28	93.3	27	90.0	1.000
Yes	2	6.7	3	10.0	
24-48 hours					
No	28	93.3	28	93.3	1.000
Yes	2	6.7	2	6.7	

FIGURE : 15



Above table and graph shows following results:
- In the early hours (0 – 4 hrs) no patients in palonosetron group had vomiting , while 2 patients (6.7%) who received granisetron had a bout of vomiting (p = 0.472).
- In 4 -12 hrs period, 2 patients(6.7%) in both the groups had incidence of vomiting (p= 1.000).
- In 12 – 24 hrs period, 2 patients(6.7%) in palonosetron group and 3patients (10 %) in granisetron group had incidence of vomiting (p = 1.000).
- In 24 – 48 hrs period, 2 patients (6.7%) in both the groups had incidence of vomiting (p= 1.000).
- Above results shows no clinical and statistical difference between the two groups in the prevention of incidence of vomiting.

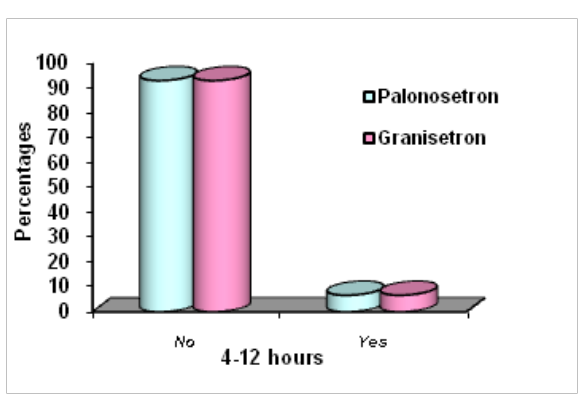


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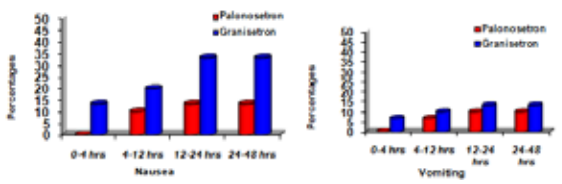
Table 11: Cumulative frequency and percentage of Incidence Of Nausea and Vomiting

	Palonosetron (n=30)		Granisetron (n=30)		P value
	No	%	No	%	
Nausea					
0-4 hours	0	0.0	4	13.3	0.112
4-12 hours	3	10.0	6	20.0	0.472
12-24 hours	4	13.3	10	30.0	0.067+
24-48 hours	3	10.0	9	33.3	0.052+
Vomiting					
0-4 hours	0	0.0	2	6.7	0.492
4-12 hours	2	6.7	3	10.0	1.000
12-24 hours	3	10.0	4	13.3	1.000
24-48 hours	3	10.0	4	13.3	1.000



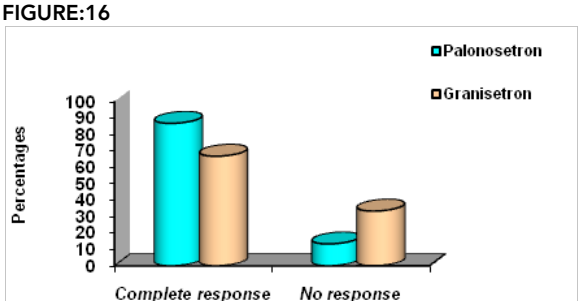
The incidence of nausea was significantly more with patients who received granisetron than when compared with patients who received palonosetron during delayed PONV period (12 – 48 hrs).

No statistically significant difference is present between palonosetron group and granisetron group for the prevention of vomiting both during early and delayed PONV period.

Table 12: Frequency and percentage of response

Response	Palonosetron (n=30)		Granisetron(n=30)		P value
	No	%	No	%	
Complete response (CR)	26	86.7	20	66.7	0.067
No response	4	13.3	10	33.3	

FIGURE:16

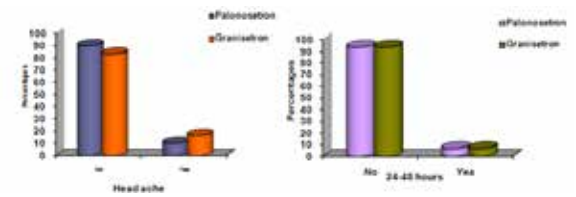


- From the above table, 26 patients (86.7%)out of the 30 patients who received palonosetron had complete response as compared to 20 patients (66.7%) who received granisetron.
- This implies , incidence of complete re sponse is significantly more associated with palonosetron (p = 0.067) com pared with granisetron.

Table 13: Incidence of Side effects

Side effects	Palonosetron		Granisetron		P value
	No (n=30)	%	No (n=30)	%	
Head ache					
No	27	90.0	25	83.3	0.706
Yes	3	10.0	5	16.7	
Constipation					
No	27	90.0	27	90.0	1.000
Yes	3	10.0	3	10.0	
Dizziness					
No	28	93.3	28	93.3	1.000
Yes	2	6.7	2	6.7	

FIGURE : 17



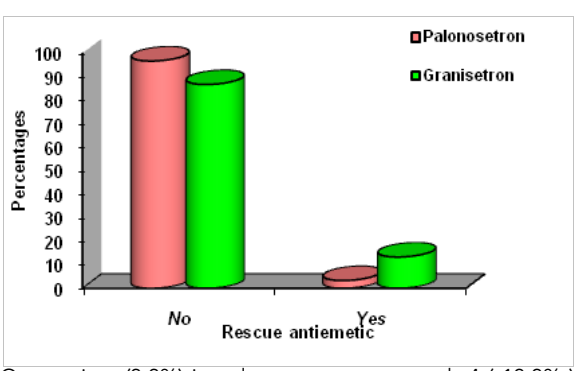
Occurrence of complications like headache, constipation and dizziness, in those patients who received palonosetron are 10%, 10% and 6.7% respectively compared to 16.7 %, 10 % and 6.7% in those patients who received granisetron.

There was no statistical significant difference in the incidence of side effects between two groups and over all incidence of side effects was found to be low.

Table 14: Rescue antiemetic

Rescue antiemetic	Palonosetron		Granisetron		P value
	No (n=30)	%	No (n=30)	%	
No	29	96.7	26	86.7	0.353
Yes	1	3.3	4	13.3	

FIGURE : 18



One patient (3.3%) in palonosetron group and 4 (13.3%) patients in granisetron group received antiemetic postoperatively.

Need of rescue antiemetic is more in granisetron group compared to palonosetron group clinically, even though statistically insignificant (p = 0.353).

Statistical Methods[45, 46, 47]:
Descriptive statistical analysis has been carried out in the

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present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, **Assumptions: 1.**Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Sample Size estimation

1.Chi-Square Test: The chi-square test for independence is used to determine the relationship between two variables of a sample. In this context independence means that the two factors are not related. In the chi-square test for independence the degree of freedom is equal to the number of columns in the table minus one multiplied by the num

ber of rows in the table minus on,

$$\chi^2 = \frac{\sum(Oi - Ei)^2}{Ei}, \text{ Where}$$

Oi is Observed frequency and

Ei is Expected frequency

With (n-1) df

The Assumptions of Chi-square test, The chi square test, when used with the standard approximation that a chi-square distribution is applicable, has the following assumptions:

- Random sample – A random sampling of the data from a fixed distribution or population.
- Sample size (whole table) – A sample with a sufficiently large size is assumed. If a chi square test is conducted on a sample with a smaller size, then the chi square test will yield an inaccurate inference. The researcher, by using chi square test on small samples, might end up committing a Type II error.
- Expected Cell Count – Adequate expected cell counts. Some require 5 or more, and others require 10 or more. A common rule is 5 or more in all cells of a 2-by-2 table, and 5 or more in 80% of cells in larger tables, but no cells with zero expected count. When this assumption is not met, Fisher Exact test or Yates' correction is applied.

2.Fisher Exact Test: The Fisher Exact Test looks at a contingency table which displays how different treatments have produced different outcomes. Its null hypothesis is that treatments do not affect outcomes-- that the two are independent. Reject the null hypothesis (i.e., conclude treatment affects outcome) if *p* is "small".

The usual approach to contingency tables is to apply the χ^2 statistic to each cell of the table. One should probably use the χ^2 approach, unless you have a special reason. The most common reason to avoid χ^2 is because you have small expectation values

	Class1	Class2	Total
Sample1	a	b	a+b
Sample2	c	d	c+d
Total	a+c	b+d	n

2x2 Fisher Exact Test

statistic=

$$\sum p = \frac{(a+b)!\,(c+d)!\,(a+c)!\,(b+d)!}{n!}\,\frac{1}{\sum a!\,b!\,c!\,d!}$$

3. Student t test (Two tailed, independent)

Assumptions: Subjects are randomly assigned to one of two groups. The distribution of the means being compared are normal with equal variances.

Test: The hypotheses for the comparison of two independent groups are:

H_o: $u_1 = u_2$ (means of the two groups are equal)

H_a: u_1 u_2 (means of the two group are not equal)

The test statistic for is t, with $n_1 + n_2 - 2$ degrees of freedom, where n_1 and n_2 are the sample sizes for groups 1 and 2. A low p-value for this test (less than 0.05 for example) means that there is evidence to reject the null hypothesis in favor of the alternative hypothesis. Or, there is evidence that the difference in the two means are statistically significant. The test statistic is as follows

t-Test: Two-Sample Assuming Equal Variances

$$S_p = \sqrt{\frac{(n_1-1)S_1^2 + (n_2-1)S_2^2}{n_1+n_2-2}}$$

In all work with two-sample t-test the degrees of freedom or df is:

$$df = n_1 + n_2 - 2$$

The formula for the two sample t-test is:

$$T = \frac{\overline{X} - \overline{Y}}{S_p\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

Pre-test: Test for variance assumption: A test of the equality of variance is used to test the assumption of equal variances. The test statistic is F with n_1-1 and n_2-1 degrees of freedom.

$$T = \frac{\overline{X} - \overline{Y}}{\sqrt{\frac{S_X^2}{n_1} + \frac{S_Y^2}{n_2}}}$$ Assuming Unequal Variances

Note in this case the Degree of Freedom is measured by

$$df' = \frac{\left(\frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}\right)^2}{\frac{\left(\frac{S_1^2}{n_1}\right)^2}{n_1 - 1} + \frac{\left(\frac{S_2^2}{n_2}\right)^2}{n_2 - 1}}$$

and round up to integer.

Results of the t-test: If the p-value associated with the t-test is small (< 0.05), there is evidence to reject the null hypothesis in favor of the alternative. In other words, there is evidence that the means are significantly different at the

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significance level reported by the p-value. If the p-value associated with the t-test is not small (> 0.05), there is not enough evidence to reject the null hypothesis, and you conclude that there is evidence that the means are not different.

4. Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)

* Moderately significant (P value:0.01<P ≤ 0.05)

** Strongly significant (P value : P≤0.01)

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

DISCUSSION

Before 19thcentury the main goal of surgeons and perioperative physicians was to give patient, a painless surgery and amnesia for the event. In the later half of 19th century with the invention of anaesthetic agents like nitrous oxide, chloroform and ether, along with painless surgery and amnesia other associated morbidities like post operative nausea and vomiting , post operative pain, infection, psychological outcome came in to focus.

PONV continues to be one of the most common complaints following surgery, occurring in more than 30% of surgeries or as high as 70% to 80% in certain high risk population without prophylaxis[43]. PONV is also one of most common reasons for patients' poor satisfaction during post operative period. PONV is of multi factorial origin, which is activated by a range of factors before anaesthesia (Female gender, surgical pathology, obesity), during anaesthesia (volatile anaesthetic agents, opioids) and after anaesthesia(post operative pain, opioids). Despite advances in antiemetic therapy in the last decade, PONV is still found to be relatively high.

5- HT_3 receptor stimulation is the primary event in the initiation of vomiting reflex. These receptors are situated on the nerve terminal of the vagus nerve in the periphery and centrally on the chemoreceptor trigger zone (CTZ) of the area postrema. Anaesthetic agents initiate the vomiting reflex by stimulating the central 5- HT_3 receptors on the CTZ and also by releasing serotonin from the enterochromaffin cells of the small intestine and subsequent stimulation of 5 -HT_3 receptors on vagus nerve afferent fibres.

The incidence of PONV after laparoscopic surgery is high (40 -75%)[42].The etiology of PONV after laparoscopic surgery is complex and is dependent on a variety of factors including age, obesity, a history of previous PONV, surgical procedure, anaesthetic technique, and post operative pain.

In our study we have compared prophylactic antiemetic therapy between granisetron and palonosetron (5-HT_3 antagonists) for the prevention of PONV in patients undergoing elective laparoscopic surgeries. We have avoided results getting affected by demographic factors (age, weight etc.) by randomizing all patients in to two groups group 'G' (granisetron) and Group 'P'(palonosetron).

Granisetron is effective for the treatment of emesis induced by cancer chemotherapy[43]. The precise mechanism of granisetron for the prevention of PONV remains unclear, but it has been suggested that granisetron may act on sites containing 5-HT_3 receptors with demonstrated antiemeticeffects[44]. Palonosetron is a unique 5 -HT_3 receptor antagonist approved for the prevention of chemotherapy induced nausea and vomiting. It is a novel 5- HT_3 receptor antagonist with a greater binding affinity and longer biological half life than older 5-HT_3 receptor antagonists[9]. The exact mechanism of palonosetron in the prevention of PONV is unknown but palonosetron may act on the area postrema which contain a number of 5- HT_3 receptors[10]. Therefore, the possible mechanism of this antiemetic for preventing PONV is similar to that of granisetron.

The effective dose of granisetron used for this study for the prevention of PONV was 40 µg/ kg. Y fujji et al demonstrated that granisetron is superior to metoclopramide in prevention of PONV after general anaesthesia and optimum antiemetic dose is 40 µg/ kg[30]. However, the dose of palonosetron to be used for the prevention of PONV is not established but was extrapolated from the dose used in the clinical trials. Kovac LA and Colleagues demonstrated that palonosetron 75µg is the more effective dose for the prevention of PONV after major gynaecological and laparoscopic surgery than 25µg and 50µg[39].

Our study demonstrated that complete response (no PONV and rescue medication) for those patients who received granisetron 40µg/ kg were 86.66%, 80%, and 66.66% between 0 to 4hrs, 4 to 12 hrs and 12 to 24 hrs, respectively and those patients who received palonosetron 0.075mg were 100%, 86.66%, and 90% between 0 to 4 hrs, 4 to 12 hrs and 12 to 24 hrs respectively.

In the study conducted by Candiotti and colleagues, observed complete response of 43% between 0 to 24hrs in patients who received palonosetron 0.075mg before induction, compared with 26 % of complete response in patients who received placebo[40].

In the study conducted by Kovac and colleagues, they found complete response of 56% (p= 0.001) in patients who received 0.075 mg between 0 to 24 hrs[39].

The difference in the results between our study and the study conducted by Candiotti and colleagues and Kovac and colleagues is probably due to their study results are observed between 0 - 24 hrs as a whole and in our study groups the study period is divided in to 0 - 4 hrs, 4 – 12 hrs and 12 – 24 hrs and the difference in the results may also be due to the time of injecting the study drug.

In the study conducted Candiotti and colleagues and Kovac and colleagues, the study drug was injected before induction of the anaesthesia, where as in our study, study drug was given 10 minutes before extubation.

In the study conducted by Bhattacharjee and colleagues, they found complete response of 90 % each in patients who received palonosetron 0. 075mg between 0 to 3 hrs, 3 to 24 hrs and 24 to 48 hrs and complete response of 86.6 % , 83.3% and 66.6 % in those who received granisetron 40 µg/ kg[42].

Our results are comparable to the study conducted by Bhattacharjee and colleagues in which they found complete response of 90 % each in patients who received palonosetron 0.075mg between 0 to 3 hrs, 3 to 24 hrs and 24 to 48 hrs and complete response of 86.6 % ,

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83.3% and 66.6 % in those who received granisetron 40 µg/ kg.

Our study shows complete response of 70% with those patients who received granisetron 40 µg/ kg and 90% complete response with those who received palonosetron 0.075mg in the prevention of delayed PONV (i.e between 24 to 48hrs). This suggests that palonosetron has an antiemetic effect which lasts longer than granisetron. The exact reason for the difference ineffectiveness between granisetron and palonosetron is not known but may be related to the half lives (granisetron 8-9hrs versus palonosetron 40 hrs) and/or the binding affinities of 5-HT3 receptor antagonists.

Study by Kovac and colleagues found complete response of 70% (p=0.002) with palonosetron 0.075mg between 24 to 48 hrs, compared with 52%of complete response with placebo[39]. And also concluded that palonosetron 0.075mg was further associated with less intense nausea as compared to placebo during 0 to 24 hrs .

Study by Candiotti et al., showed complete response of 49%(p= 0.188) with palonosetron 0.075mgbetween 24 to 48 hrs, compared with 41%of complete response with placebo.[40]

In our study, cumulative complete response (between 0 – 48 hrs) for granisetron was 66.7% and palonosetron was 86.7%, comparably higher than the other studies probably due to large sample size by the above authors.

Our study shows no statistically significant difference between in the baseline values of hemodynamic variables between the two groups before, during and after giving the study drug. In PACU we have recorded the SBP, DBP and HR over a period of 30 min at regular interval. According to our study there was no hemodynamic alterations between these results.

The statistics regarding hemodynamic effects, after injecting palonosetron and granisetron could not be compared with the studies of other authors as the hemodynamic effects have not been mentioned in the study made by other authors.

Adverse effects with a single therapeutic dose of granisetron and palonosetron were not clinically serious[39]. Incidence of common side effects like dizziness and constipation were not significant in both groups but the incidence of headache is comparatively more in Group 'G'(16%) than in Group 'P' (10%) .

In the study conducted by Candiotti et al, regarding the side effects like dizziness, constipation and headache, it has been mentioned that in the placebo group incidence of side effects were more and the incidence of side effects in the study group has not been mentioned.

In the study conducted by Bhattacharjee et al, 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 the present study for Palonosetron (10%) and slightly more for granisetron (16%) not statically significant.

Use of rescue antiemetic in granisetron group was about 4 (13%) in 30 patients , where as in palonosetron group was about 1 (3.33%) in 30 patients (In the form of Inj. metoclopramide).

In the study conducted by Candiotti et al, between 0 -72 hrs showed requirement of rescue antiemetic medication about 52% in placebo group and 44% in palonosetron group with 0.075 mg.

In the study conducted by Kovac et al, between 0 -72 hrs showed requirement of rescue antiemetic medication about 46% in placebo group and 27% in palonosetron group with 0.075 mg.

The difference in need for rescue antiemetic between our study and Candiotti et al or Kovac et al studies probably due to the requirement of rescue antiemetic in the later part of their observation(beyond 48 hrs) as the clinical effects of the antiemetic study drug will gradually be reduced beyond 48 hrs.

In the study conducted by Bhattacharjee et al, there was no requirement of rescue antiemetics for both palonosetron group and granisetron group, their observation were 0% in both the groups. These results are almost in agreement with our study for Palonosetron group (3%) and slightly more for granisetron group (13.3%) statically not significant.

Updated guidelines for managing postoperative nausea and vomiting were recently announced at the 2008 Annual meeting of American society of anaesthesiologist in Pennsylvania .

"All suggest titrating the use of prophylactic antiemetic strategies according to clinical needs. Clinical needs are determined by a patient's risk for PONV that is best estimated using a validated risk score.

In general, no preventive measures are needed when the risk is low. At moderate risk, one or two antiemetic preventions are often felt appropriate, and when the risk is high or very high, a combination of two or more antiemetic strategies is usually recommended.

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".

They emphasise on the usage of the 5HT3 antagonists. These guidelines also suggest a potential benefit of combination prophylaxis in patients, at high risk of PONV.

CONCLUSION

This study concludes that the prophylactic intravenous administration of palonosetron is more effective than granisetron for controlling postoperative nausea and vomiting with less incidence of side effects.

Safety profile for side effects is more with palonosetron and it is more potent than granisetron in preventing PONV.

So we observed minimal emetic and nauseating episodes in post operative period in patients who had received i.v palonosetron 0.075mg in comparison to those patients who received i.v granisetron 4oµg/kg , under going laparoscopic surgery under general anaesthesia.

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