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A COMPARATIVE CLINICAL EVALUATION REGARDING EFFICACY BETWEEN ONDANSETRON AND APREPITANT IN PREVENTION OF POST-OPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING GENERAL ANAESTHESIA FOR LAPAROSCOPIC CHOLECYSTECTOMY OPERATION

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Abstract

Background: post operative nausea and vomiting is one of the commonest and unpleasant complications encountered. delays in the discharge of patients. It is often associated with complications like dehydration ,haematoma formation,wound dehiscence resulting in prolonged hospital stay. This study aimed to compare the effect of aprepitant and ondansetron, for prevention of postoperative nausea and vomiting in patients after laparoscopic cholecystectomy

Materials and methods: This randomised double blinded study included patients (aged 18–60years) who underwent laparoscopic cholecystectomy under general anaesthesia. Patients were divided into two groups,group A and B(60 patients in each group) receiving single dose of ondansetron(8mg) and aprepitant(80mg) respectively. Incidence and extent of nausea and vomiting, use of rescue antiemetics and number of post operative nausea and vomiting episodes in both the drug groups were assessed at 0,1,12,24 and 48 hours after the operation.

Results: In patients receiving aprepitant(Group B) post operative nausea and vomiting were less in 1^{st},12^{th},24^{th} and 48^{th} post operative hours than in the patients receiving ondansetron(Group A)

Conclusion: It was found that aprepitant was better than ondansetron in effectively reducing PONV in these patients undergoing laparoscopic cholecystectomy in the 1,12,24 and 48 hours hrs after the surgery .

Keywords: Aprepitant, Laparoscopic Cholecystectomy, Ondansetron, Vomiting

Introduction

Postoperative nausea and vomiting (PONV), defined as nausea and or vomiting occurring within 48 hours after surgery, affects between 20 and 30 percent of post operative patients (1). Apart from some patient specific risk factors like age, sex, basal metabolic index, history of motion sickness and previous history of nausea and vomiting, the duration of surgery and anaesthesia administration also affects the incidence and severity of post operative nausea

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and vomiting. Moreover, there are few types of surgery like middle ear operations and laparoscopic procedures which may result in accentuation of this postsurgical vomiting episodes. PONV is one of the most important and common cause of post operative morbidity which is quite evident from the facts that it may lead to serious postoperative complications like dehydration, haematoma formation, wound dehiscence, aspiration pneumonities and increased hospital stay with resultant increase in the effective treatment cost[2].

Several drugs like metoclopramide, droperidol, dexamethasone etc have been used in the management of this condition. The most favoured drug for the prophylaxis of PONV in anaesthetic practice is the prototypical $5HT_3$ receptor antagonist, ondansetron [3]. Despite proper administration of antiemetic prophylaxis with intravenous 5HT3 receptor antagonists or other similar drugs, 30–40% of the patients still experience postoperative nausea and vomiting (4). Thus, an unmet medical need for improved PONV prophylaxis exists.

A new class of drug known as non-peptide neurokinin1 (NK1) receptor agonists has demonstrated activity against both peripheral and central emetic stimuli in animal models.(5,6,7) Consistent with the idea that antagonism at the NK1 receptor could affect the response to emetic stimuli, evidence suggesting the potential efficacy of NK1 receptor antagonists against PONV was first obtained in clinical trials of two different drugs in this class, which were assessed in patients undergoing major gynaecological surgery.(8,9,10,11). Aprepitant is the first NK_1 receptor antagonist available for clinical use as an antiemetic (12). As an individual drug or a part of combination therapy with other antiemetics, aprepitant is approved for use and recommended in consensus guidelines for the prevention of chemotherapy induced nausea and vomiting (CINV) and the clinical profile of aprepitant suggests that it may provide benefit against PONV as well(13,14)

Laparoscopic procedures are one of the most regularly performed surgeries worldwide and amongst them laparoscopic cholecystectomy is one of the commonest surgical intervention. Pneumoperitoneum, during laparoscopy, can stimulate the vagus, nerve thereby increasing chances of post surgical nausea and vomiting(15).

There has been few studies worldwide showing that Aprepitant is more effective than the conventional and commonly used standard antiemetic drugs for control of post operative nausea and vomiting. Hence the present study was conducted to find out results in a regional population in terms of controlling post operative nausea and vomiting following laparoscopic cholecystectomy by comparing antiemetic effects of the standard used drug ondansetron and the upcoming drug for such use,aprepitant.

METHODOLOGY

MATERIALS & METHODS

The present study is a prospective , randomised double blinded study. After obtaining approval from the institute's ethical committee, the study has been carried out in the Department of Anaesthesiology in ESI PGIMSR hospital for a period of 1 year (2019 -2020) . Altogether 120 patients scheduled for elective laparoscopic cholecystectomy were enrolled in the study. After their hospital admission, details of the study were explained to

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the eligible patients and information sheets were given to them and informed consent was obtained from those who were willing to participate in the study on the day of the surgery.

Inclusion factor for the study were patients of both the sexes scheduled for laparoscopic cholecystectomy belonging to American Society of Anaesthesiologist's physical status one or two, between the age of 18 and 60 years.

Patients with known allergy to the study drugs and those who are on medicines like Pemozide, Cisapride, Astemizole, Warfarin , any hormonal contraceptives or any other anti emetic drugs were excluded from the study. American society of Anaesthesiologist's physical status three or any pregnant or lactating women were also not included in the study population.

The randomisation schedule was a computer generated random sequence which was instructed to an in house physician who was not involved with the study. Both the study drugs for administration along with matching placebos were kept ready. Sealed envelopes with randomisation codes were prepared for sorting the patients into two study groups. On the day of surgery the patients where randomly allocated into two groups after opening the sealed envelopes with the randomisation codes inside.

In the morning of the scheduled surgery patients received the study drugs according to the randomised codes they received in sealed envelopes. As the study was double blinded, patients belonging to one group received a placebo tablet within three hours before the start of surgery and intravenous drug Ondansetron(8mg) within one hour before the commencement of operation while the other group received tablet Aprepitant 80mg within three hours before start of the operation and a placebo injection within one hour of beginning of the surgery.

.On arrival to the operation theatre, intravenous cannulation was done and routine monitoring devices were attached to monitor heart rate, Spo2, blood pressure, ecg, etco2 and core temperature. A standard general anaesthetic technique was used. After completion of the surgery, residual neuromuscular blockage was antagonized by neostigmine and glycopyrrolate in appropriate and proportional doses. After that the patients were shifted to post-surgical care unit and were monitored for next 48 hours.

Post operative data collection was blinded. The incidence of PONV, severity of nausea, and the need for rescue antiemetics were evaluated for 48 h at the end of following hours after surgery : 1,12,24,48 hrs.

Few functional definitions -

An episode of vomiting - defined as either vomiting (expulsion of stomach contents) or retching (an involuntary attempt to vomit but not productive of stomach contents).

VRS scale - The intensity of nausea episode was assessed using an elevan point verbal rating score (VRS), patients rated nausea from 0 (no nausea) to 10 (nausea as bad as it could be) at 0, 1, 12 , 24, and 48 h after operation. Patients were asked to evaluate their maximal degree of nausea during the interval assessments and received rescue antiemetics on basis of that.

Rescue medication for PONV (dexamethasone 4mg as an initial rescue drug, metoclopramide 10 mg as a second rescue drug) were used upon patient request or complaint of established nausea (VAS score >4) or vomiting.

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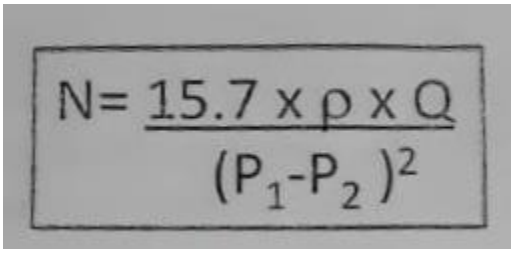
Adverse events were evaluated and recorded by the investigator during the entire observation period.

The primary outcome measure of this study was the incidence of nausea and vomiting during the first 48h after operation, and the secondary outcome measures were the severity of nausea, need for rescue medication.

STUDY POPULATION: Calculation of study population is determined by the formula



Where,

. P1 and **P2** are the proportions of the 2 groups

. p is the average of **P**1 and **P**2

. Q is **100- p**

By this formula putting the values of previously conducted study we can get the approximate sample size. The value of N came out to be 59.60043. So we are taking 60 patients in each group i.e. 120 patients in total were included into the study.

120 ASA 1 and ASA 2 female patients scheduled for laparoscopic cholecystectomy operation under General anaesthesia.

SAMPLE SIZE: 120 patients divided into two groups

1. Group A: Preoperative IV Inj Ondansetron 8 mg
2. Group B: Preoperative Tab Aprepitant 80 mg

STATISTICAL ANALYSIS:

Patients Name, Age, Sex, Weight, ASA physical status were noted.

Variables such as Age, Sex, ASA status and incidence of Nausea and/or Vomiting were noted at 0 hr, 1st hr, 12th hr, 24th hr and 48th hr after shifting the patient from Post-Anaesthesia Care Unit to the Surgical ward. Individual observations were noted on case sheets, which was then compiled into a 'Master Chart' with Microsoft Excel 2019 (version 2007 Build 13029.20344). The data has been analysed with IBM SPSS Statistics 25.

The two groups were Group A and Group B.

All the Numerical Data was checked for Normality with Shapiro Wilk test. If found Normal, Mean and SD was calculated for each group. Levene-F test was done to check for Homogeneity of variances. Independent Samples T Test was used to analyse data.

If not found to be Normal, Mann Whitney U test was conducted to analyse data. Mean Rank and Sum of Ranks were also noted.

Non Parametric data was analysed by Mann Whitney U test.

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Chi Square Test was used to analyse the Sex and ASA PS of the patients.
The results with p value < 0.05 would be considered significant

RESULTS

Table 1

DEMOGRAPHICS	GROUP A	GROUP B	p-value
AGE(years)[mean(SD)]	47.30 (1.02)	49.52 (1.24)	0.0509
FEMALE	40	36	>0.05
MALE	20	24	
ASA Ⅰ	31(51.7%)	32(53.3%)	>0.05
ASA Ⅱ	29(48.3%)	28(47.7%)	

1.Table 1A
GROUP-SEX cross-tabulation

		Group * Sex Cross-tabulation			
			Sex		Total
			F	M	
Group	A	Count	40	20	60
		% within Group	66.7%	33.3%	100.0%
		% within Sex	52.6%	45.5%	50.0%
		% of Total	33.3%	16.7%	50.0%
	B	Count	36_a	24_a	60
		% within Group	60.0%	40.0%	100.0%
		% within Sex	47.4%	54.5%	50.0%
		% of Total	30.0%	20.0%	50.0%
Total		Count	76	44	120
		% within Group	63.3%	36.7%	100.0%
		% within Sex	100.0%	100.0%	100.0%
		% of Total	63.3%	36.7%	100.0%

Table 1A showing cross-tabulation of sex in two test groups

ANALYSIS

It is seen from the tables (table1A) that in Group A 20 patients(33.3%) were male and 40 patients (66.7%) were females. In Group B 24 patients (40%) were males and 36 patients (60%) were females.

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ASSOCIATION

Association of sex versus group was not statistically significant. (p-value > 0.05)

AGE GROUP CROSS-TABULATION

Table 1B GROUP STATISTICS OF DISTRIBUTION OF AGE IN YEARS (N=120) IN TWO GROUPS

Distribution of age (in years) in two groups								
	Group	Mean	Standard deviation	Minimum	Maximum	Independent-Samples Mann-Whitney U Test		
						MannWhitney U	Standardized Test Statistic (z-value)	Significance (p value)
Age	A	47.30	1.027	32	61	2065.00	1.393	.162
	B	49.52	1.240	32	65			

Analysis:

1. Independent Sample Mann-Whitney U Test was applied and Null hypothesis was retained i.e.

distribution of age (in years) were comparable in both the groups at all intervals. (p value is 0.164).

Table 2: Patients (Group A and B) experiencing post operative nausea in different time periods:

	Group A		Group B		P value	Level of Significance
	Number	Percentage	Number	Percentage		
0 hour	12	20%	5	8.3%	0.114	P > 0.05
0-1 hour	17	28.3%	6	10%	0.019	P < 0.05
1-12 hour	18	30%	6	10%	0.011	P < 0.05

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12-24 hour	11	18.3%	3	5%	0.043	P < 0.05
24-48 hour	6	10%	0	0%	0.027	P < 0.05

Table 3: Patients (Group A and B) experiencing post operative vomiting in different time periods:

	Group A		Group B		P value	Level of Significance
	Number	Percentage	Number	Percentage		
0 hour	8	13.3%	1	1.7%	0.032	P < 0.05
0-1 hour	12	20%	2	3.3%	0.008	P < 0.05
1-12 hour	14	23.3%	3	5%	0.007	P < 0.05
12-24 hour	8	13.3%	1	1.7%	0.032	P < 0.05
24-48 hour	6	10%	0	0%	0.027	P < 0.05

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Figure 1

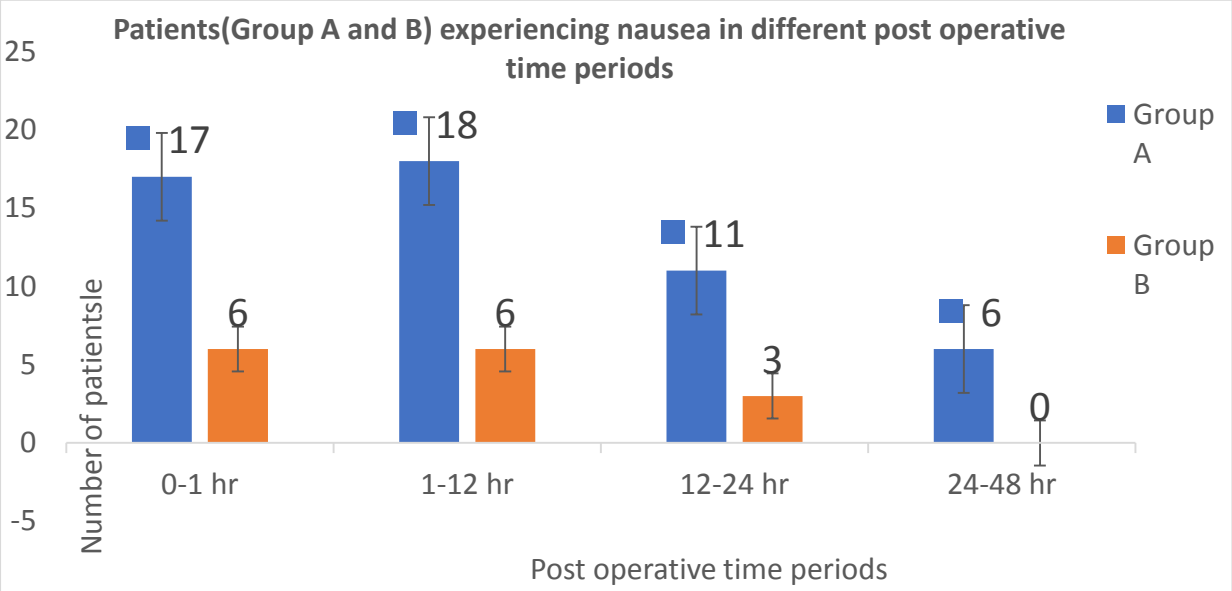

Figure 2

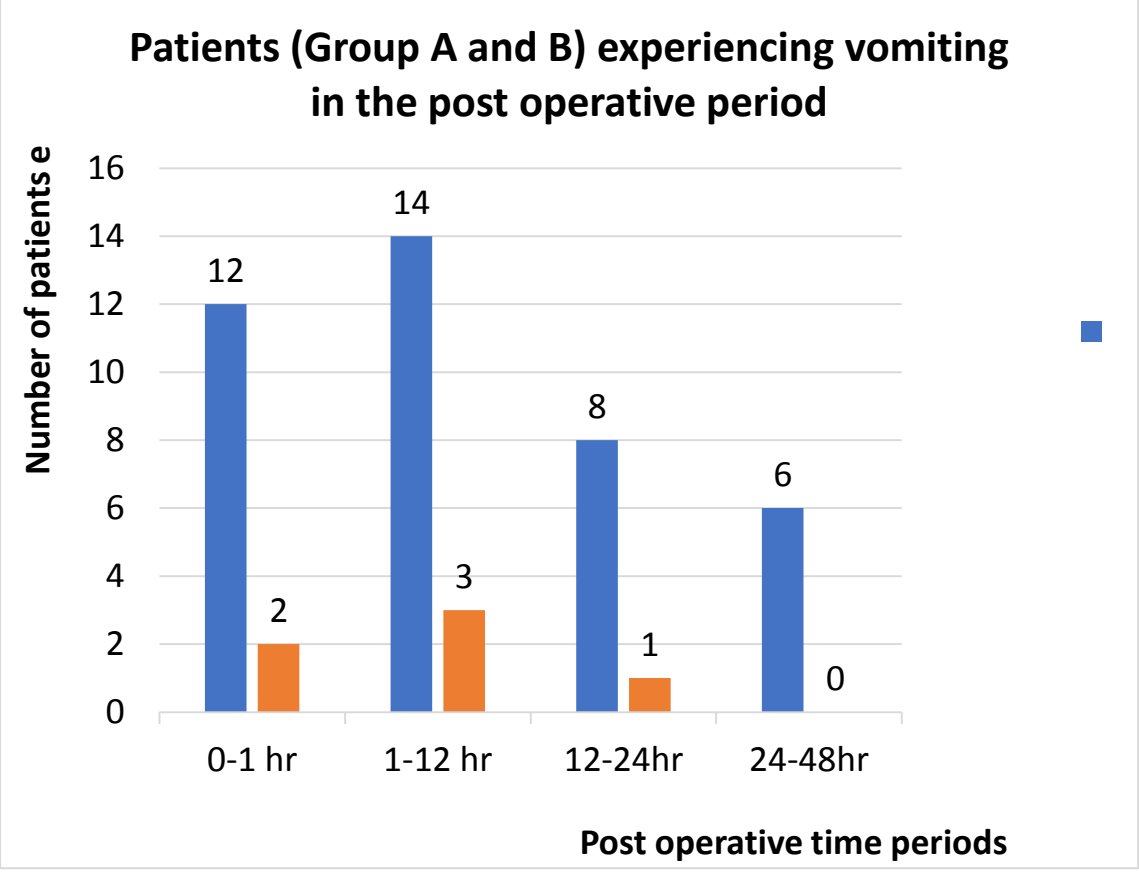

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Table 4: Patients requiring antiemetic in different post operative time periods:

	Group A		Group B		P value	Level of Significance
	Number	Percentage	Number	Percentage		
0-1 hour	3	6.25	1	2.08	0.307	P > 0.05
1-12 hour	14	23.33	3	5.00	0.007	P < 0.05
12-24 hour	9	15.00	1	2.08	0.005	P < 0.05
24-48 hour	8	13.33	1	1.7%	0.032	P < 0.05

Table 5

Variables	Group A		Group B		P value	Level of Significance
Peak Nausea VRS score (0-10)	Median score (interquartile range)	Percentage	Median score (interquartile range	Percentage		
0-24H	4(0-8)		1(0-4)			P > 0.05
24-48H	2(0-6)		0(0-2)			

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Table 6

Post operative Time Periods(h)		0-1H			1-12H			12-24H			24-48H		
		Group A (number and percentage)	Group B (number and percentage)	P	Group A (number and percentage)	Group B (number and percentage)	P	Group A (number and percentage)	Group B (number and percentage)	P	Group A (number and percentage)	Group B (number and percentage)	P
Vomiting Episodes	0	48	58		46	57		52	59		54	60	
	1-2	9	2		9	2		6	1		5	0	
	>2	3	0		5	1		2	0		1	0	
Nausea VRS	0	43	54		42	54		49	57		54	60	
	1-4	12	5		11	5		8	3		5	0	
	>4	5	1		7	1		3	0		1	0	

Table 7 Adverse effects

Adverse Effects	GROUP A		GROUP B	
	Number	Percentage	Number	Percentage
Dizziness	2	4.17	1	2.08

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Diarrhoea	1	2.08	0	0
Constipation	2	4.17	1	2.08
Sedation	1	2.08	0	0
Itching/redness	2	4.17	1	2.08
Others	0	0.00	0	0.00

DISCUSSION

Despite new advances in anaesthesia and the introduction of new class of anti emetics, post operative nausea and vomiting(PONV) is still one of the most common post operative patient complaints. About 30% of patients receiving general anesthesia are affected and the incidence is known to rise up to 80% or more in patients having high risk for post operative nausea and vomiting. In addition to other patient specific risk factors, few types of surgery also contribute to increased risk. Laparoscopic procedures involves creating a pneumoperitoneum, often stimulating the vegas nerve which results in increased incidences and severity of post surgical nausea and vomiting(15).

Apart from the conventional anti emetic drug groups used to manage PONV like dopamine D2 antagonists (metoclopramide) and 5Ht3 antagonists(ondansetron, ramosetron) a new class of drugs known as non peptide neurokinin one receptor antagonist (NK1 RA) has demonstrated activity against both peripheral and central emetic stimuli. Aprepitant is the first NK1 receptor antagonist available for clinical use as an antiemetic and it has been effectively used to treat chemotherapy induced vomiting. In few studies aprepitant have shown promising results in controlling post operative nausea and vomiting compared to many standard and the emetic drugs.(16,17,18,19)

In view of the above information the present study was formulated to compare the antiemetic effect of the NK1 RA aprepitant and a commonly used 5HT3 antagonist ondansetron

In our study, the distribution of age, sex and ASA physical status among patients of both the groups (Group A receiving intravenous ondansetron and Group B receiving tab aprepitant) was found to have no significant association with post operative nausea and vomiting and the results were comparable between the two groups. In this study the statistical tests that were used to evaluate the effectiveness of the drugs have shown that aprepitant(group B) have significantly reduced incidences and severity of post operative nausea and vomiting episodes compared to ondansetron(group A) in the time periods 0,1,12,24 and 48 hours following surgery. Our study also demonstrated that the patients receiving aprepitant (group B) not only required rescue antiemetics after a longer time period postoperatively but also the number of patients requiring rescue antiemetics was significantly less compared to patients

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receiving ondansetron (group A). Incidences of adverse effects like headache, dizziness, diarrhoea, sedation etc were found to be comparable between the two groups.

Diemunsch.P et al and later Gan et al concluded in their study that 40 mg and 125mg of oral aprepitant was significantly more effective than oral 4mg ondansetron for preventing vomiting at 24 and 48 hours post operatively in patients undergoing abdominal surgery and it significantly reduced severity of nausea in the first 48 hours after surgery. This demonstration was similar with the findings of our study.

Jeyabalan S et al used 40 mg aprepitant against 8 mg ondansetron and the result was comparable in terms of effectiveness to treat post operative nausea and vomiting. This was unlike our study where we used a higher dose i.e. 80mg of aprepitant against 8mg I.V. ondansetron and found a statistically significant difference between the effectiveness of aprepitant and ondansetron with the former showing a much better efficacy in reducing the incidence of nausea and vomiting in the subsequent post operative time periods.

Lim CS et al ,Sinha AC et al and Ham SY et al used a combination of oral aprepitant (80 mg) and ondansetron against a monotherapy of ondansetron where they confirmed that the group receiving aprepitant was significantly better in terms of post surgical nausea and vomiting. This result further supports the result of our study. In 2021 Safarnejad F et al had demonstrated that 80mg of aprepitant was significantly more effective in controlling post operative nausea and vomiting compared to 8mg of intravenous ondansetron. They also found out that the group receiving aprepitant required less amount of rescue antiemetic drug over 48 hours post operatively to that compared with the group receiving ondansetron. These findings further substantiated the results of our present study.

SUMMARY

There have been new advances in anesthesia and the introduction of a new class of antiemetics, post-operative nausea and vomiting (PONV) is still one of the most common postoperative patient complaints. About 30% of patients receiving a general anesthetic are affected and the incidence is known to rise up to 80% or more in high-risk patient groups. Numerous studies have investigated the administration of different antiemetics to reduce the incidence of PONV but, still, there is controversy on the optimal approach. The study was aimed to compare the therapeutic efficacy between Tab Aprepitant 80 mg and Tab Ondansetron 8 mg in prevention of Post-operative Nausea and vomiting in patients undergoing General anaesthesia for laparoscopic cholecystectomy operation and requirement of any rescue anti-emetic during the study of these 2 drugs.

After obtaining the approval of institute ethical committee this study was conducted as a randomized prospective comparative study in two groups of 60 patients each, a total of 120 patients undergoing General anaesthesia for laparoscopic cholecystectomy operation. Then the patients were randomized into two groups. One group received Pre-operative Ondansetron and another group received pre-operative Aprepitant 2 hours before the induction of anaesthesia. We used a standardized technique for anaesthesia with volatile anaesthetics and without Propofol as it's anti-emetic action may hinder with the results. In the post-operative period these patients were monitored for incidence of nausea and vomiting and rescue anti-emetics were given

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accordingly. The incidence of nausea and vomiting and use of rescue anti-emetics were noted on 0, 1st, 12th, 24th and 48th hours. Statistical analysis was done with SPSS26 software and result was analyzed.

It's evident from the histograms, diagrams and tables that Oral Aprepitant was superior to oral Ondansetron in terms of controlling the post-operative nausea and vomiting in patients undergoing general anaesthesia for Laparoscopic Cholecystectomy operation. We can also see that the consumption of rescue anti-emetics were less in the patients who received preoperative Aprepitant than in patients receiving pre-operative Ondansetron. As no serious adverse effects were encountered during the study of the two drugs, we can conclude that oral Aprepitant can be used safely in peri-operative period for prevention of post-operative nausea and vomiting.

CONCLUSION

This prospective study aimed towards evaluating and comparing the efficacy of Aprepitant and Ondansetron in terms of preventing post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy operation.

Aprepitant was better than Ondansetron in terms of controlling post-operative nausea and vomiting both from 0 to 48 hours post-operatively and their difference was significantly more. Aprepitant appeared to be more effective in controlling post-operative nausea and vomiting on 24th to 48th post-operative period than on 0 to 24th post-operative period. So conclusion can be made that Aprepitant was superior to Ondansetron in achieving better response for 48 hours in controlling post-operative nausea and vomiting.

The patients were followed up until their complete hospital stay in post-operative period. Moreover the requirement for rescue anti-emetics was found to be less in the group receiving aprepitant in comparison to the group receiving ondansetron.Adverse effects were comparable in the post-operative period in patients of both groups.

The study showed that Pre-operative oral Aprepitant was superior to pre-operative Ondansetron in a surgical population who received volatile anaesthetics for Laparoscopic cholecystectomy operation.

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