

# APREPITANT Vs RAMOSETRON-THEIR ROLE IN THE PREVENTION OF POST OPERATIVE NAUSEA & VOMITING IN PATIENTS UNDERGOING ABDOMINAL SURGERIES UNDER GENERAL ANAESTHESIA-A RANDOMISED CONTROLLED STUDY

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## ABSTRACT

**Background:** Post operative nausea and vomiting is one of the commonest and unpleasant complications encountered and often cause delay 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 ramosetron, for prevention of postoperative nausea and vomiting in patients after intra-abdominal surgeries.

**Materials and methods:** This randomised double blinded study included patients who underwent intra-abdominal surgeries under general anaesthesia. Patients were divided into two groups,group A and B(22 patients in each group) receiving oral aprepitant(80mg) and single dose of intravenous ramosetron(0.3mg) 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 12,24 and 48 hours after the operation.

**Results:** In patients receiving aprepitant(Group A) incidence and severity of post operative nausea and vomiting were found to be comparable to the same in the patients receiving ramosetron(Group B) in 12th,24th and 48th post operative hours.

**Conclusion:** It was found that Aprepitant and Ramosetron had comparable efficacy in preventing PONV upto 48 hrs post operatively in patients having abdominal surgeries under general anaesthesia ,as well as in aspects of causing adverse effects. Number of patients who experienced nausea and vomiting postoperatively were less in the Group A population(Aprepitant group ) compared to the patients in Group B(Ramosetron group).

**Keywords:** Aprepitant, ramosetron, Postoperative nausea and vomiting (PONV)

## **INTRODUCTION**

Post operative nausea and vomiting have always been regarded as one of the troublesome and dreaded complications . Postoperative nausea and vomiting (PONV) is defined as any nausea, retching, or vomiting occurring during the first 24-48 hours after surgery in patients. It is one of the most common cause of patient dissatisfaction after anaesthesia, with reported incidences of 30% in all post – surgical patients and upto 80% in high-risk patients(1).Despite new advances in anaesthesia with the introduction of different classes of antiemetics post operative nausea and vomiting(PONV) is still one of the most common post operative complaints(1)

PONV complicate post-operative care in several ways like electrolyte disturbance and dehydration, aspiration of vomitus and wound dehiscence due to frequent expulsive efforts, associated with delayed recovery and prolonged hospital stay.(2,3,4)

PONV is multifactorial and among the many factors, female gender, past history of PONV and motion sickness, use of opioids, nitrous oxide and non-smoking history are the independent predictors for PONV [5,6]. There are certain types of surgery which poses greater risk, for example in adults most of the PONV incidences are found in intra abdominal surgeries, laparoscopic surgeries, major gynaecological surgeries, ENT surgeries. PONV after inter abdominal surgeries may be due to vagal afferent stimulation due to gut manipulation which may also get stimulated due to inflation of peritoneal cavity by CO<sub>2</sub> insufflation.

The most favoured group of intraoperative drugs for the prophylaxis of PONV are 5HT<sub>3</sub> receptor antagonists like the prototypical ondansetron or the longer acting ramosetron. Ramosetron ,a 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) receptor antagonist is effective and safe without serious adverse effects in terms of prevention of post operative nausea and vomiting<sup>(6)</sup> It is more potent and has longer lasting anti-emetic effects than Ondansetron because of a slower rate of dissociation from the target receptor and higher binding affinity<sup>(7)</sup>.

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.(8,9,10) 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.(11,12,13,14). Aprepitant is the first NK1 receptor antagonist available for clinical use as an antiemetic (15). 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(16,17)

Despite proper administration of antiemetic prophylaxis with intravenous 5HT<sub>3</sub> receptor antagonists or other similar drugs, 30–40% of the patients still experience postoperative nausea and vomiting (18). Thus there is still an unmet medical need for improved PONV prophylaxis . Hence we chose the new group of drug Aprepitant to be compared with a relatively commonly used antiemetic drug Ramosetron for the prophylaxis of PONV in patients undergoing abdominal surgeries under general anaesthesia.

## AIMS AND OBJECTIVES

### **Aims**

- 1.To compare the relative efficacy of Oral Aprepitant 80mg and Intravenous Ramosetron 0.3mg in reducing the incidence of PONV in postoperative patients undergoing general anaesthesia for abdominal surgeries.
- 2.To observe for any adverse effect of drugs in the patients of the study
- 3.To assess need for any rescue antiemetic during study of these drugs.

### **Objectives**

To analyse the incidence of nausea and vomiting and consumption of rescue antiemetics in A and B groups where Cap Aprepitant and intravenous Ramosetron are used as antiemetics.

## METHODOLOGY

**Study design:** Randomized, prospective, double-blind study.

**Study setting:** ESI PGIMSR, Manicktala, Kolkata.

**Study area:** Operation Theatre –General Surgery and Gynaecology, post surgical ITU, Surgical Ward, Maternity Ward in ESI PGIMSR, Manicktala, Kolkata.

**Study population:** 44 ASA 1 & ASA 2 patients scheduled for abdominal surgery under General Anaesthesia.

### **SAMPLE SIZE :**

The working formula for estimating minimum sample size in each group from proportion data is determined by:

$$N = \frac{15.7 \times \rho \times Q}{(P_1 - P_2)^2}$$

Where,

- $P_1$  and  $P_2$  are the proportions of the 2 groups
- $\rho$  is the average of  $P_1$  and  $P_2$
- $Q$  is  $100 - \rho$

[ $P_1$  = No-nausea proportion in Aprepitant Group,  $P_2$  = No-nausea proportion in Ramosetron group]

Feeding the available data from the above two studies into the equation gives us,  $P_1 = 83.6$  and  $P_2 = 42.0$

Thus, the calculated value for  $N$  is 21.19. We take 22 patients in each group using a systematic random sampling method.

**Group- A:** preoperative cap Aprepitant 80 mg

**Group- B:** intra operative iv Ramosetron 0.3mg

**STUDY PERIOD:** April 2020 to March 2021.

**Inclusion criteria:**

- 1) Patients with age between 20 to 45 years, undergoing abdominal surgeries.
- 2) Operation duration between 30 min to 4 hours.
- 3) Patients with ASA 1 & ASA 2 status.

**Exclusion criteria:**

- 1) Patients not willing to participate in the study.
- 2) Patients known to be allergic to the drugs used in the study like Aprepitant, Ramosetron.
- 3) Pregnant and lactating patients.
- 4) Patients with severe hepatic dysfunction that can interfere with metabolism of Aprepitant.
- 5) Patients with history of QT prolongation or taking other medicines that leads to QT prolongation.
- 6) Patient receiving drugs like Pimozide, Terfenadine, Astemizole, Cisapride which are known CYP3A4 Inhibitor.
- 7) Patients receiving warfarin & other anti- coagulants & anti- platelet.
- 8) Patients on hormonal contraceptives.
- 9) Patients with chronic alcohol abuse, drug abuse, chronic opioid use, patient with history of vomiting or taking antiemetic within 24 hrs before surgery.

**Sampling technique:** Simple Random Sampling.

**Study technique:-**

After approval of the College Ethical Committee, 44 ASA1 & 2 patients aged between 20-45 yrs, planned for major abdominal surgery under general anaesthesia were included in this study. Patients were randomized on simple random sampling by RPG simple dice (Android App version) on smart phone for generating random numbers between 1 & 6. Patients were allocated to group A if he / she rolled on even number (2/4/6) and in group B if he/she rolled on odd number (1/3/5).

1. Group A – Patients received pre- operative capsule Aprepitant 80 mg 3 hrs before induction of anaesthesia.
2. Group B— Patients received inj Ramosetron 0.3 mg just after induction of anaesthesia.

The day before operation consent for the study was taken from each patient in the language he/ she understands after proper explanation.

All patients were on NPM ( nothing per mouth) from midnight on the day of operation. On the day of operation each patients received inj Pantoprazole 40 mg i.v in the morning. Three hours before induction , one group ( Gr A) was given 80 mg oral Aprepitant & other group (Gr B) was given no antiemetic drug pre operatively. Then the patients were brought to pre- recovery room. An i.v line established & drip started. Pulse oximeter , BP cuff, ECG leads attached .

Each patient was premedicated with 0.15 mg/kg inj Midazolam in recovery 30mins before induction.

Then the patient was pre oxygenated for 3 min with 100% O<sub>2</sub> in OT. General Anaesthesia was performed using inj Sodium Thiopentone(2.5%) 3-4 mg/ kg (until the abolition of eyelash reflex), inj Fentanyl 2 mcg/kg & Rocuronium 0.6-1mg/kg. Maintenance was done by 0.7 to 0.9 MAC by sevoflurane& lungs ventilated with 33% oxygen and 67% nitrous oxide to maintain an end- tidal carbon- dioxide of 35-45 mmHg. All the patients of Group B received IV Ramosetron 0.3mg just after induction. Group A patients received no anti emetic drug in the intra- operative period. Inj Neostigmine with inj Glycopyrrolate were used as reversal. Before tracheal extubation , oral cavity & oro-pharynx suction was done with suction catheter. In post- operative period the patients were monitored in recovery room or post- anaesthesia care unit for 30 mins & need of any rescue anti emetic drug was noted in both group of patients. After that the patients were shifted to post-surgical care unit and afterwards ward. All patients were monitored for total 48 hrs.

1<sup>st</sup> line rescue antiemetic is inj Ondansetron 4mg i.v.(maximum 3 doses)

### 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. 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

**Table: Association between patients having post operative nausea (PON) at 12 hrs(R12) of post operative time : Group**

GROUP			
R12 PON	Group-A	Group-B	TOTAL
<b>No</b>	17	14	31
Row %	54.8	45.2	100.0
Col %	77.3	63.6	70.5
<b>Yes</b>	5	8	13
Row %	38.5	61.5	100.0
Col %	22.7	36.4	29.5
<b>TOTAL</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

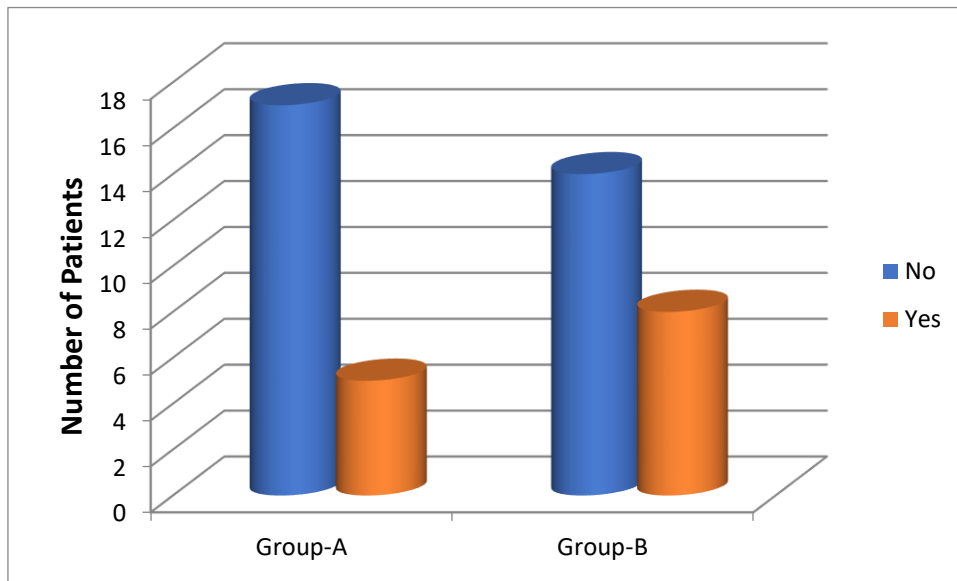
**Chi-square value:** 0.9826; **p-value:** 0.3215

**Odds ratio:** 1.9429 (0.5177,7.2908)

In Group-A, 5 (22.7%) patients had post operative nausea at 12hrs after operation.

In Group-B, 8 (36.4%) patients had post operative nausea at 12hrs after operation.

Association of presence of post operative nausea at 12 hrs vs. both the drug Groups was not statistically significant (p=0.3215).



**Table: Association between patients having post operative nausea (PON) at 24 hrs(R24) of post operative time: Group**

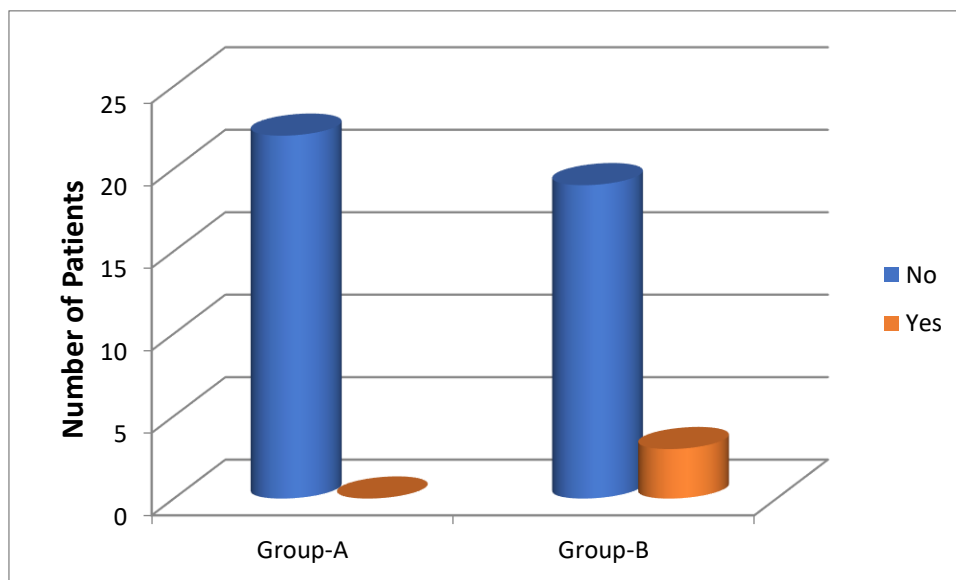
GROUP			
R24 PON	Group-A	Group-B	TOTAL
<b>No</b>	22	19	41
Row %	53.7	46.3	100.0
Col %	100.0	86.4	93.2
<b>Yes</b>	0	3	3
Row %	0.0	100.0	100.0
Col %	0.0	13.6	6.8
<b>TOTAL</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

Chi-square value: 3.2195; p-value: 0.0727

In GroupA no patients had post operative nausea at the 24 hrs interval after operation.

In Group-B, 3 (13.6%) patients had post operative nausea at 24hrs .

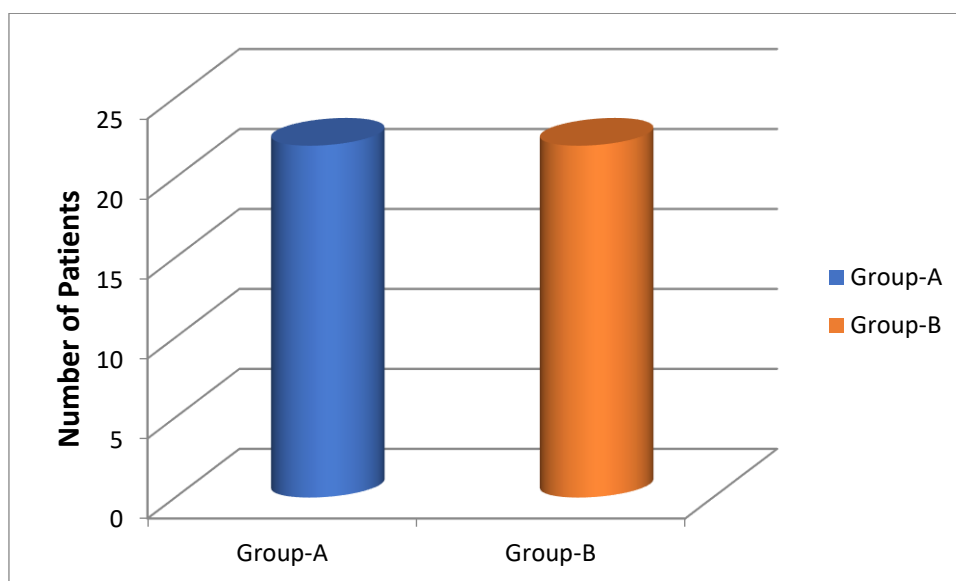
Association of presence of post operative nausea at 24hrs vs. both the drug Groups was not statistically significant (p=0.0727).



**Table: Association between patients having post operative nausea (PON) at 48 hrs(R48) of post operative time : Group**

GROUP			
R48 PON	Group-A	Group-B	TOTAL
<b>No</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
<b>TOTAL</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

In Group-A and group B no patients had post operative nausea after 48hrs .



**Table: Association between patients having post operative vomiting (POV) at 12 hrs(R12) of post operative time : Group**

GROUP			
R12 POV	Group-A	Group-B	TOTAL
<b>No</b>	20	17	37
Row %	54.1	45.9	100.0
Col %	90.9	77.3	84.1
<b>Yes</b>	2	5	7
Row %	28.6	71.4	100.0
Col %	9.1	22.7	15.9
<b>TOTAL</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

**Chi-square value:** 1.5290; **p-value:**0.2162

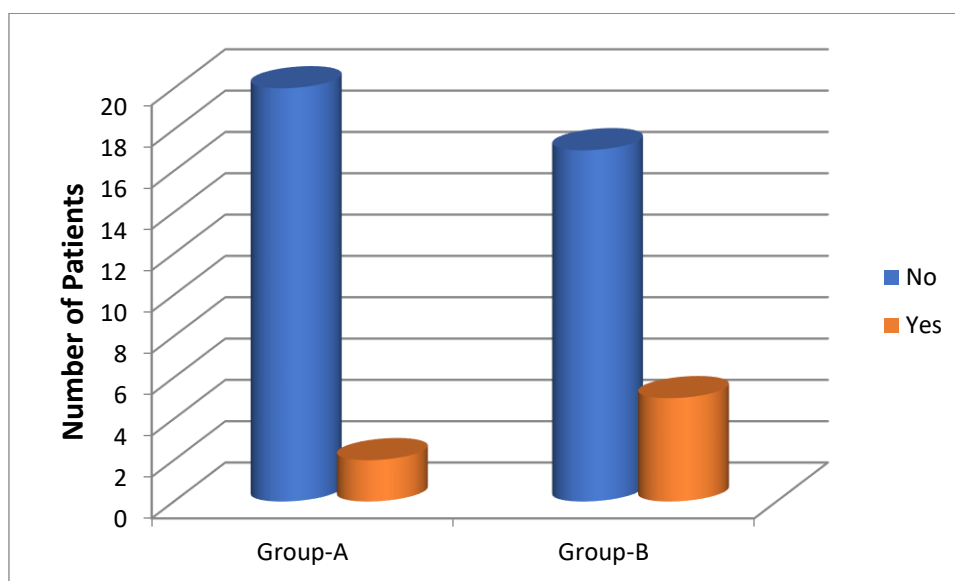
**Odds ratio:**2.9412 (0.5046,17.1419)

In Group-A, 2 (9.1%) patients had post operative vomiting at the 12 hrs interval after operation .

In Group-B, 5 (22.7%) patients had post operative vomiting at the 12 hrs interval after operation .

Association of presence of post operative nausea at 12 hrs vs. both the drug Groups was not statistically significant (p=0.2162).





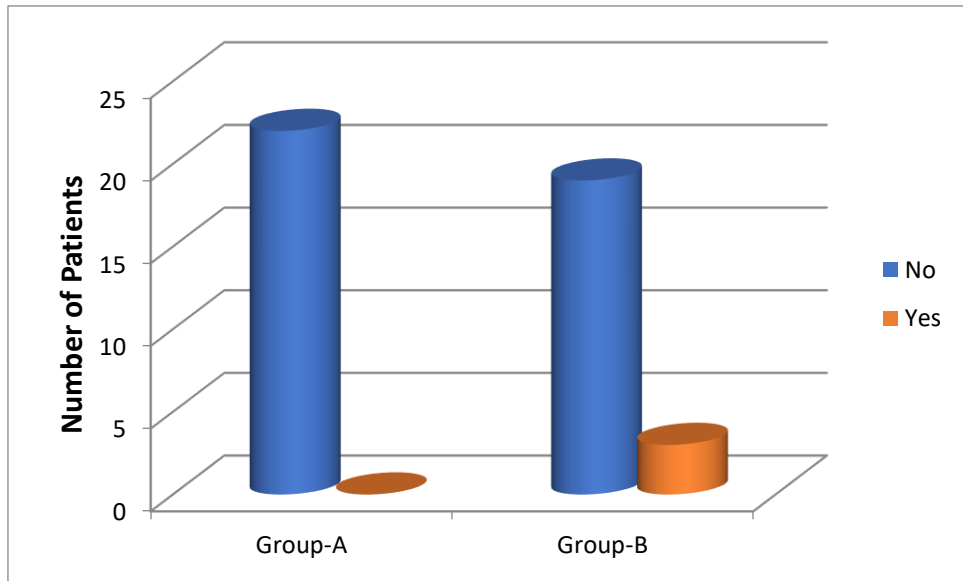
**Table: Association between patients having post operative vomiting (POV) at 24 hrs(R24) of post operative time : Group**

GROUP			
R24 POV	Group-A	Group-B	TOTAL
<b>No</b>	22	19	41
Row %	53.7	46.3	100.0
Col %	100.0	86.4	93.2
<b>Yes</b>	0	3	3
Row %	0.0	100.0	100.0
Col %	0.0	13.6	6.8
<b>TOTAL</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

**Chi-square value: 3.2195; p-value:0.0727**

In Group-B, 3 (13.6%) patients had post operative vomiting after 24hrs of operation.

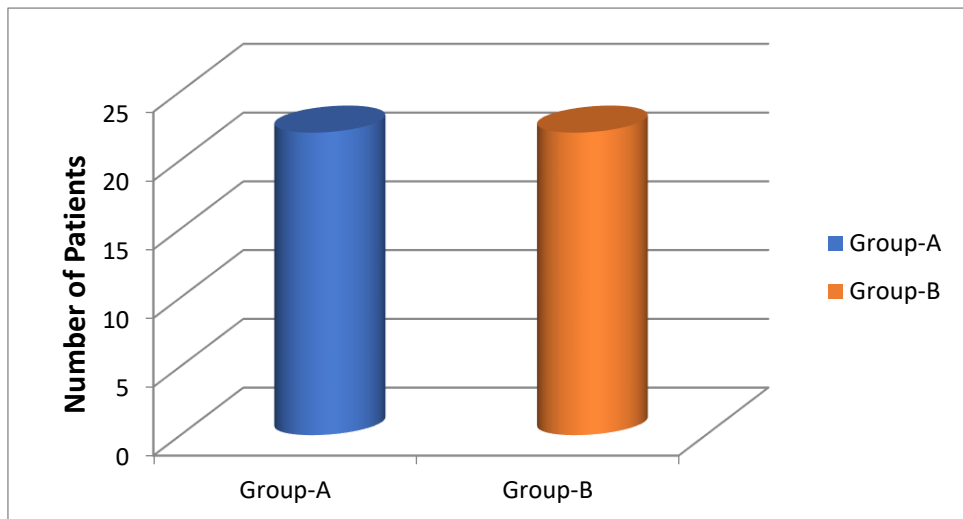
Association of presence of post operative vomiting at 24 hrs vs. both the drug Groups was not statistically significant (p=0.0727).



**Table: Association between patients having post operative vomiting (POV) at 48 hrs(R48) of post operative time: Group**

GROUP			
R48 POV	Group-A	Group-B	TOTAL
<b>No</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
<b>TOTAL</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

In Group-A and Group B no patients had vomiting 48hrs postoperatively.



**Table: Association between Rescue drug (Rsc D) at 12hrs post operative time : Group**

GROUP			
Rsc D Ryes12	Group-A	Group-B	TOTAL
<b>No</b>	16	14	30
Row %	53.3	46.7	100.0
Col %	72.7	63.6	68.2
<b>Yes</b>	6	8	14
Row %	42.9	57.1	100.0
Col %	27.3	36.4	31.8
<b>TOTAL</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

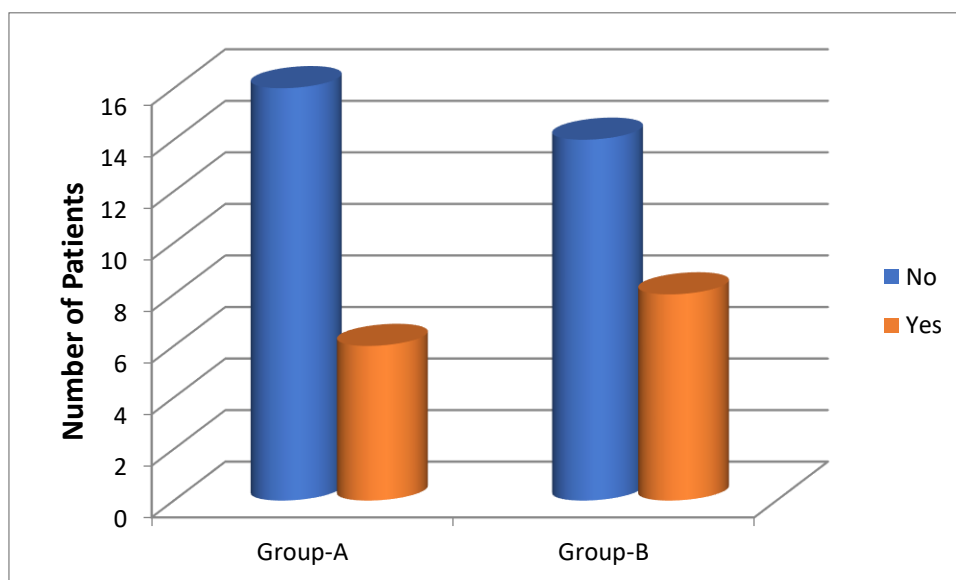
**Chi-square value: 0.4190; p-value:0.5174**

**Odds ratio:1.5238 (0.4242,5.4732)**

In Group-A, 6 (27.3%) patients required rescue antiemetic drug 12 hrs post operatively

In Group-B, 8 (36.4%) patients required rescue antiemetic drug 12 hrs post operatively

Association of requirement of Rescue drug(Rsc D ) after 12 hrs of operation vs. Groups ,was not statistically significant (p=0.5174).



**Table: Association between Rescue drug (Rsc D) at 24hrs post operative time: Group**

GROUP
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Rsc D R24	Group-A	Group-B	TOTAL
<b>No</b>	22	18	40
Row %	55.0	45.0	100.0
Col %	100.0	81.8	90.9
<b>Yes</b>	0	4	4
Row %	0.0	100.0	100.0
Col %	0.0	18.2	9.1
<b>TOTAL</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

Chi-square value: 4.4000; p-value:0.0359

In Group-B, 4 (18.2%) patients needed Rsc drug at 24 h post operative time.

Association of requirement of Rescue drug(Rsc D ) after 24 hrs of operation vs. Groups ,was statistically significant (p=0.0359).

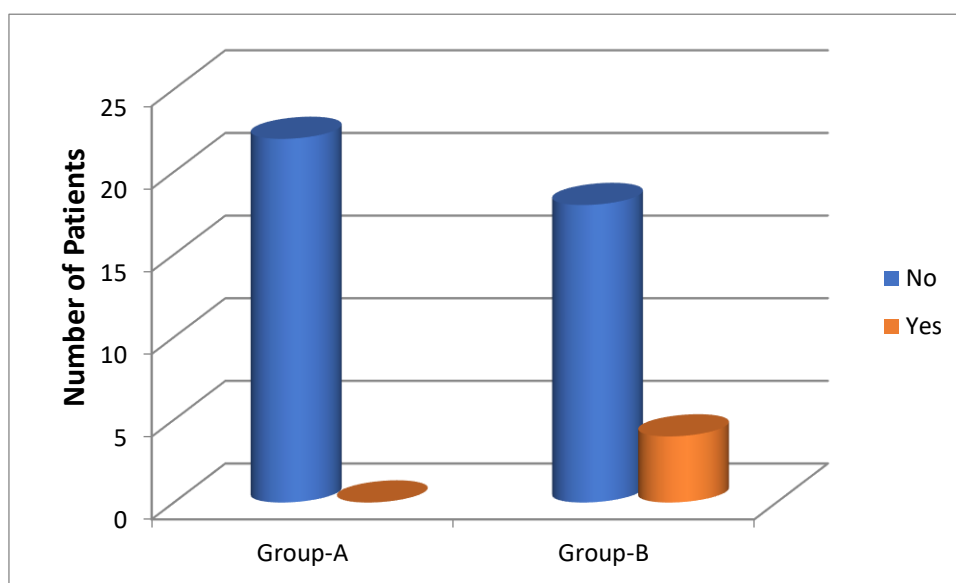


Table: Association between Rescue drug (Rsc D) at 48hrs post operative time: Group

GROUP			
Rsc D R48	Group-A	Group-B	TOTAL
<b>No</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
<b>TOTAL</b>	22	22	44
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

After 48hrs of operation (R48) no patients of either Group A or Group B needed rescue antiemetic drugs

## DISCUSSION

Post operative nausea and vomiting (PONV) is defined as nausea with or without vomiting that occurs within 48 hours of surgery. It takes place in 20 to 30% of post operative patients, the incidence rises to 70 to 80% in high risk patients. The incidence of PONV is very frequent from 60 to 80% without any prophylactic anti emetic therapy particularly in laparoscopic, middle ear and abdominal surgeries. PONV causes complications like dehydration, electrolyte imbalance, problems with oral drug therapy, delayed mobility and recovery after surgery. Even morbidities like aspiration pneumonitis can happen. Various anti emetic preparations for prevention of PONV are being continuously tried to achieve reasonable success.

The present study was done to compare the efficacy of NK1 receptor antagonist aprepitant and 5HT3 receptor antagonist ramosetron. Total 44 patients were taken in this study and divided in 2 groups.

Group A(22 patients) :Aprepitant 80mg pre operatively

Group B(22 patients) :Ramosetron 0.3mg IV intraoperatively

In our study, the distribution of age, sex and ASA physical status among patients of both the groups (Group A receiving cap Aprepitant and Group B receiving IV Ramosetron ) 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 A) had reduced incidences and severity of post operative nausea and vomiting episodes compared to ramosetron( group B) in the time periods 0,12,24 and 48 hours following surgery but the difference was not statistically significant . Our study also demonstrated that the number of patients requiring rescue antiemetics was less in patients receiving aprepitant (GroupA) compared to patients receiving ramosetron (Group B) but again differences between the two groups were found to be statistically non significant except in one postoperative interval i.e 24 hrs after surgery where the difference was found to be statistically significant. This study also found that aprepitant and ramosetron have comparable antiemetic effect for longer period of time (till 48 hours post operative time monitored)and both of them were safe with minimum adverse effects.

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(19). 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(20). These two studies and few more alike used Aprepitant in doses of 80 mg for PONV prevention which yielded better results with no compromise in the safety profile. In our study too we used 80mg of Aprepitant versus 0.3mg of Ramosetron for PONV prevention and found effective yet comparable results.

Lee SJ et al <sup>21</sup> (2012) showed that this the incidence of nausea was significantly lower in the aprepitant group (50.0%) compared to the control group (80.9%) during the first 24 hours following surgery. The incidence of vomiting was significantly lower in the aprepitant group (4.7%) compared to the control group (42.8%) during the first 24 hours

following surgery. In addition, the severity of nausea was less among those in the aprepitant group compared with the control group over a period of 24 hours post-surgery ( $P < 0.05$ ). Lee further concluded that aprepitant plus ramosetron was more effective than ramosetron alone in reducing the incidence of PONV and use of rescue antiemetics in first 24 hrs postoperatively. Our study did not have a control group or a combined drug group but this study demonstrated that both Aprepitant and Ramosetron effectively reduced incidence of PONV and although number of patients with incidences of PONV were less in the Aprepitant group compared to the ramosetron group, their difference was not statistically significant

However a study with larger sample size needs to be conducted to further establish this finding.

### **Limitations**

Despite every effort, this study has got some limitations.

1. The study has been done in a single centre.
2. The sample size was small.
3. The study was done in a tertiary care hospital where hospital bias is a possibility
4. Some biochemical parameters of nausea and vomiting like CRP, Urea, ketones have not been estimated.

### **SUMMARY**

Post operative nausea & vomiting is still one of the troublesome complaints in spite of recent advances in anaesthesia. Amongst the patients receiving general anaesthesia 30% are affected and in high risk population the incidence may rise to 80% or more. There have been lots of studies to investigate the effects of different antiemetics for reduction of PONV but satisfactory outcomes are yet to come.

The study was aimed to compare the therapeutic efficacy between Tab Aprepitant 80 mg and injection Ramosetron 0.3 mg in prevention of Post-operative Nausea and vomiting in patients undergoing abdominal surgeries under general anaesthesia 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 22 patients each, a total of 44 patients undergoing General anaesthesia for abdominal surgeries. Then the patients were randomized into two groups. One group received Pre-operative Aprepitant 3 hours before the induction of anaesthesia and another group received per-operative Ramosetron IV. We used a standardized technique for anaesthesia with volatile anaesthetics and without Propofol as its 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 accordingly. The incidence of nausea and vomiting and use of rescue anti-emetics were noted on 12<sup>th</sup>, 24<sup>th</sup> and 48<sup>th</sup> hours. Statistical analysis was done with SPSS 27 software and result was analyzed.

It's evident from the histograms, diagrams and tables that oral Aprepitant was superior to injection Ramosetron 0.3 mg in terms of controlling the post-operative nausea and vomiting in patients undergoing general anaesthesia for abdominal surgeries. Need for rescue antiemetics was less in aprepitant group than in ramosetron group. No serious adverse effect was found in both the groups. In our study we found that oral aprepitant had comparable effects with that of injection ramosetron in terms of efficacy in prevention of PONV and causing any adverse events.

## CONCLUSION

It can be inferred from our study that Aprepitant and Ramosetron had comparable efficacy in preventing PONV upto 48 hrs post operatively in patients having abdominal surgeries under general anaesthesia ,as well as in aspects of causing adverse effects. Number of patients who experienced nausea and vomiting postoperatively were less in the Group A population(Aprepitant group ) compared to the patients in Group B(Ramosetron group).

**Declaration of conflicting interest:** The authors declare that there is no conflict of interest.

**Funding:** This study received no specific grant from any funding agency.

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