

Efficacy of Ramosetron and Ondansetron in Preventing Postoperative Nausea and Vomiting in Patients Undergoing Middle Ear Surgery Following General Anesthesia: A Prospective, Randomized, Double Blind Study

Dr. Bhabananda Mukhopadhyay¹, Dr. Samapika Mandal^{2*}

¹Associate Professor, Department of Anaesthesiology, ESI Post Graduate Institute for Medical Science and Research, 54bagmari road, Ghose Bagan, Kolkata, West Bengal 700054, India

²Senior Resident, Department of Anaesthesiology, North Bengal Medical College and Hospital, North Bengal, Siliguri, West Bengal 734012, India

DOI: [10.36347/sasjm.2020.v06i03.004](https://doi.org/10.36347/sasjm.2020.v06i03.004)

| Received: 03.03.2020 | Accepted: 10.03.2020 | Published: 19.03.2020

*Corresponding author: Dr. Samapika Mandal

Abstract

Original Research Article

Background: Postoperative nausea and vomiting (PONV) is a very common and distressing complication after anaesthesia and surgery and 60-80% of patients who undergo middle ear surgery experience this complication. The multifactorial nature of PONV have hampered development of an effective antiemetic therapy and the 5-Hydroxytryptamine (5-HT₃) receptor antagonists are currently recommended as the agents of first choice to prevent PONV. Ramosetron is a relatively new, selective 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonist that reportedly has more potent antiemetic effects compared with other 5-HT₃ receptor antagonists. The purpose of this study was to evaluate and compare the efficacy of ramosetron for the prevention of postoperative nausea and vomiting (PONV) with that of Ondansetron in patients undergoing middle ear surgery after general anaesthesia. **Objective:** To compare the antiemetic efficacy of prophylactic Ondansetron with Ramosetron. **Methods:** In this prospective, randomized, double-blinded study, 96 patients of either sex, aged 18-60 years of ASA physical status I and II, who were undergoing middle ear surgery under general anaesthesia were enrolled. Patients were divided into two groups: the Ramosetron group (0.3 mg i.v.; n=48), the Ondansetron group (4 mg i.v.; n=48). The incidence of PONV, severity of nausea, and the use of rescue antiemetic requirements during the first 48 h after surgery in intervals 0,6,12,24,36,48 hours were evaluated. **Statistical Analysis and Results:** Single dose of Ramosetron (0.3mg) was found to be overall more effective than single dose of Ondansetron (4mg) in prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery following general anaesthesia. Statistically significant difference between Groups A and B ($P<0.05$) was found in the time period 24-48hrs post operatively showing that Ramosetron was superior to Ondansetron as antiemetic both regarding frequency and severity. **Conclusion:** It was evident that prophylactic administration of single dose IV Ramosetron (0.3 mg) has better efficacy than single dose IV Ondansetron (4 mg) in reducing the episodes of PONV over 48 hours postoperatively in patients undergoing middle ear surgery under general anaesthesia.

Keywords: antiemetics, ondansetron, ramosetron, PONV, middle ear surgery, General Anaesthesia.

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INTRODUCTION

Postoperative nausea and vomiting (PONV) is one of the most common and distressing complications after anesthesia and surgery with an overall incidence of 20-30 percent after balanced anaesthesia approaching 70% in patients with certain high risk factors [1].

60 to 80 percent of patients who undergo middle ear surgery experience post operative nausea and vomiting [2]. Such a high incidence of post

operative nausea and vomiting associated with middle ear surgery is likely to be caused by activation of the vestibular afferent pathway which also explains the pathophysiology involved in motion sickness. This justifies the use of prophylactic antiemetic medication for prevention of PONV after middle ear surgery.

For PONV prevention selective 5 Hydroxytryptamine (serotonin) type 3 (5HT₃) receptor antagonists are considered one of the first line therapy because of their efficacy and fewer side effects

compared with other antiemetics [3]. Most research on the 5HT₃ receptor antagonists has been done on ondansetron and its anti emetic efficacy has been established in prevention and treatment of PONV [4, 5]. Ramosetron, a relatively new selective 5HT₃ receptor antagonist, exhibits significant greater binding affinity for 5-HT₃ receptors with a slower dissociation rate from receptor binding, resulting in more potent and longer receptor antagonizing effects compared to older 5-HT₃ receptor antagonists [6, 7].

There are few reports about the antiemetic effect of ramosetron compared with ondansetron for prevention of PONV in laparoscopic and ambulatory surgeries [8, 9]. However, reports showing the antiemetic efficacy of monotherapy of intravenous administration of ramosetron to prevent PONV compared with that of ondansetron in patients undergoing middle ear surgery under general anaesthesia are still less available [10, 11].

Therefore, we designed this prospective, randomized, double-blinded study to evaluate the efficacy of intravenous administration of ramosetron for

preventing PONV compared with that of ondansetron in patients undergoing middle ear surgery during the first 48 hrs after surgery.

MATERIALS & METHODS

The present study has been carried out in the department of Anaesthesiology in ESIPGIMSR Hospital for a period of 2 years (2015-2017). Altogether 96 patients were enrolled in the study.

The patients were randomised and allotted into 2 groups namely group A (patients receiving Ondansetron) and group B (patients receiving Ramosetron).

After approval from institution of ethical committee, 96 patients of ASA1 & 2 grade, age 18-60 yrs undergoing middle ear surgeries were allocated in the study. A written informed consent was obtained from each patient. The mean duration of surgery in group A was 88.44 min and in group B it was 87.2 min and patients underwent mastoidectomy or tympanoplasty.

The inclusion and exclusion factors are enlisted below -

Inclusion factors	Exclusion factors
Male: Female – 1:1	Patient refusal
Age – 18-60 years	Any known allergy to the drugs
BMI- 18.5-29.9	Pregnancy, lactation
ASA physical status grade – 1 and 2	Subjects who vomited or received antiemetics within 24 hours before surgery
	Hepatic, renal or cardiopulmonary abnormality
	Alcoholism, diabetes, significant gastrointestinal disorders (peptic ulcer, GERD)

Patients were randomly allocated to receive one of the two study medications according to a computer-generated randomized number table: group A Ondansetron group, ondansetron 4 mg i.v.; and group B Ramosetron group 0.3mg iv.

The envelopes were opened before induction of anaesthesia by a trained nurse not involved in the study. The nurse then prepared the study medications 2ml of each (no dilution required in the used doses) in identical syringes, and administered 10 min before the end of surgery. All patients, investigators collecting the postoperative data, and nurses involved in the postoperative care of patients were blinded to the randomization.

A standardized anaesthesia technique was followed. 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. The patients were preoxygenated with 100% oxygen for a period of 3 min. Injection fentanyl (2 µg/kg) and glycopyrrolate (0.01 mg/kg) were given intravenously 3 min before induction of anaesthesia. All the patients were induced with IV injection of Thiopentone Sodium 2.5% (5 mg/kg)

titrated till the loss of eyelash reflex. After that, rocuronium (1 mg/kg) was given to facilitate laryngoscopy and intubation. Controlled ventilation was maintained with 35% oxygen in 65% nitrous oxide and sevoflurane as inhalational agent (0.5-1 MAC). Laryngoscopy, intubation, and cuff inflation were completed within 1-3mins in all cases. Muscle relaxation was maintained with intermittent intravenous rocuronium (0.3 mg/kg) as and when required. Intraoperatively, the pulse rate, respiratory rate, arterial oxygen saturation, ECG, capnography, systolic and diastolic pressure were monitored continuously. Ventilation was mechanically controlled and adjusted to maintain the End tidal CO₂ pressure (E_T CO₂) between 35-45 mmHg.

By using double blinded randomization technique these patients received, group A-ondansetron 4 mg iv (2 ml) and group B-ramosetron 0.3 mg iv (2ml), within 10 min before extubation of the patient.

At the completion of surgery, residual neuromuscular blockade was antagonized at TOF ratio more than 0.7 with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg intravenously and patient was extubated in conscious condition.. The patients were

then sent to the postoperative recovery unit. Postoperative analgesia was provided with injection diclofenac 50 mg in intramuscular route and infusion of paracetamol (1gm). All patients received moist oxygen supplementation (3 l/min) for 2 h and standard minimum monitoring systems were used. All the patients were on intravenous drip and did not have any oral fluid during a period of 6 h. After surgery, patients were observed in the postanesthetic recovery room before transferring to the ward when stable.

Post operative data collection was blinded. The incidence of PONV, severity of nausea, and the need for rescue antiemetics were noted for 48 h at the end of following hours after surgery at 0,1,6,12,24,36,48 hrs. Patients were monitored every 15 min in the recovery room and every 2 hrs in the ward except when patients were asleep. Adverse events were evaluated and recorded during these periods.

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).

The intensity of nausea episode was assessed using a 100 mm visual analogue scale (VAS) (0, none; 100, maximum). 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 >50) or vomiting.

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.

Sample size was calculated on the basis of the primary outcome measure. It was estimated that 48 subjects would be required per group in PONV from the control treatment (from 50% to 17%) with 80% power and 5% probability of type one error.

Data Were Captured On Structured Case Report Forms

Numerical variables have been compared between groups by Student's t test if normally distributed, or by Mann-Whitney U test, if otherwise.

All analyses were two-tailed. Statistically significant data was implied by $p < 0.05$.

The raw data was entered into a Microsoft Excel spreadsheet and analyzed by statistical software using SPSS for Windows (version 16, SPSS Inc, Chicago, IL, USA).

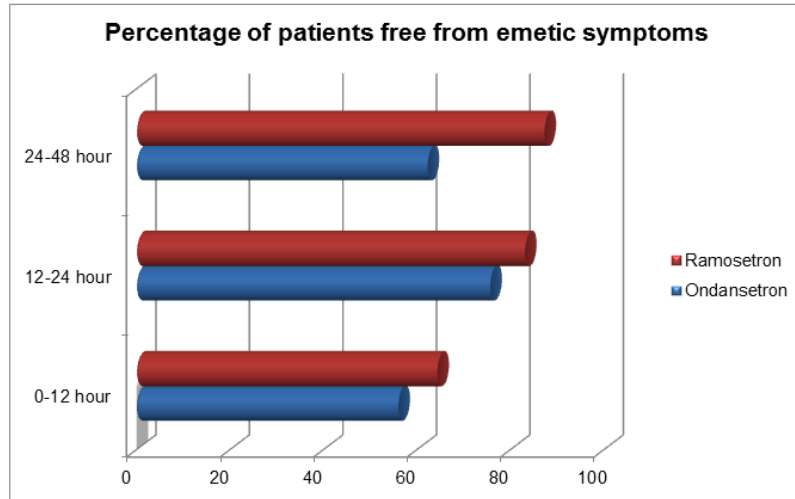
RESULTS & ANALYSIS

In the present study total number of cases were 96. These cases were divided into 2 groups each consisting of 48 cases.

- Group A of 48 patients were studied with the drug Ondansetron.
 - Group B of 48 patients were studied with the drug Ramosetron
1. Among 48 patients under Group A (ondansetron), 54% were male and 46% were female .Out of 48 patients in group B (ramosetron) 48% were male and 52% were female.
 2. Group A and Group B are comparable to each other in terms of bodyweight as difference between mean body weight of Group A and Group B were found to be insignificant.
 3. Group A and group B are comparable in terms of age as differences between their mean was found to be insignificant.
 4. Both the groups are comparable in terms of duration of anaesthesia as the differences between the mean duration of anesthesia in the two groups were found to be insignificant.
 5. Patients in Group A(ondansetron) and Group B (ramosetron) are comparable to each other in terms of duration of surgery as difference between the mean of them is found to be insignificant statistically
 6. While ramosetron was found to be more effective , percentage of patients free from emetic symptoms in both the groups were comparable in 0-24 hr period but statistically significant increase in percentage of patients were found to be free from nausea or vomiting in the time period 24-48 hrs in the ramosetron group.
 7. The incidence of nausea was significantly lower in ramosetron group in the time period 24-48hrs while the difference between two groups is not significant in 0-24 hrs time period.
 8. Significantly less number of patients suffered from vomiting in the ramosetron group in 24-48hrs while the difference is not statistically significant between the two drugs in 0-24hrs period.
 9. Rescue antiemetics were less required in the Ramosetron group but the difference between both the groups is found to be statistically significant in 24-48 hrs period.

Table-1: Patients free from emetic symptoms

	Group A		Group B		P value	Level of Significance	Complete Response Gr A	Response Gr B
	Number	Percentage	Number	Percentage				
0-12 hour	27	56.25	35	64.58	0.0873	P > 0.05	24(50%)	34(70%)
12-24 hour	35	72.91	40	83.33	0.2187		35(72%)	40(83%)
24-48 hour	30	62.5	42	87.5	0.0047	P < 0.05	25(52%)	42(87%)

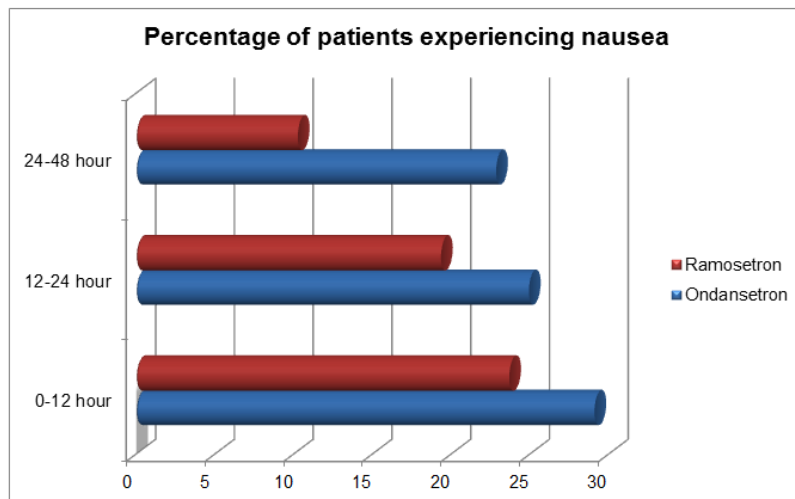


At 0-12 hr and 12-24 hr, the difference between Gr A (Ondansetron) and Gr B (Ramosetron) in case of number of patients free from post-operative emetic symptoms is statistically insignificant, but there is

statistically significant difference between Group A and Group B at 24-48 hour time period. Complete response (patients free from emetic episodes and did not need rescue antiemetic) and percentage was assessed.

Table-2: Patients experiencing nausea

	Group A		Group B		P value	Level of Significance
	Number	Percentage	Number	Percentage		
0-12 hour	14	29.16	9	18.75	0.2301	P > 0.05
12-24 hour	9	25.00	5	10.42	0.2460	
24-48 hour	11	22.92	4	8.33	0.0488	P < 0.05

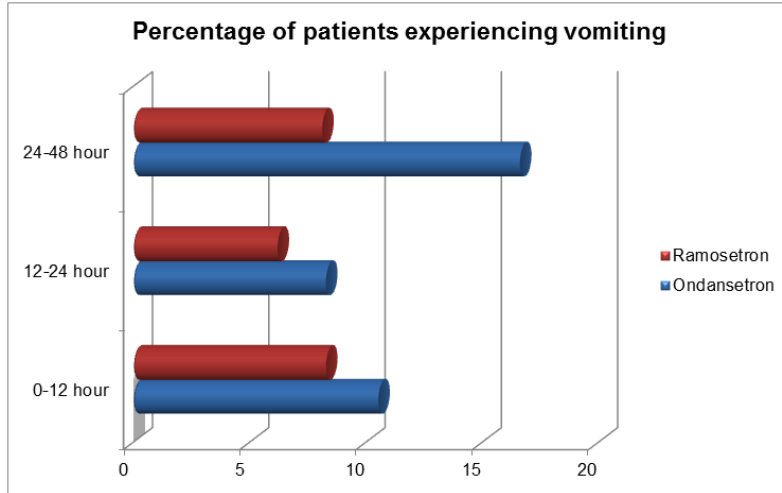


At 0-12 hr and 12-24 hr, the difference between Gr A (ondansetron) and Gr B (ramosetron) in case of number of patients experiencing nausea is statistically insignificant, but there is statistically

significant difference in patients experiencing nausea between Group A and Group B at 24-48 hour time period.

Table-3: Patients experiencing vomiting

	Group A		Group B		P value	Level of Significance
	Number	Percentage	Number	Percentage		
0-12 hour	7	14.58	4	8.33	0.3371	P > 0.05
12-24 hour	4	8.33	3	6.25	0.6965	
24-48 hour	8	16.67	2	4.17	0.0455	P < 0.05

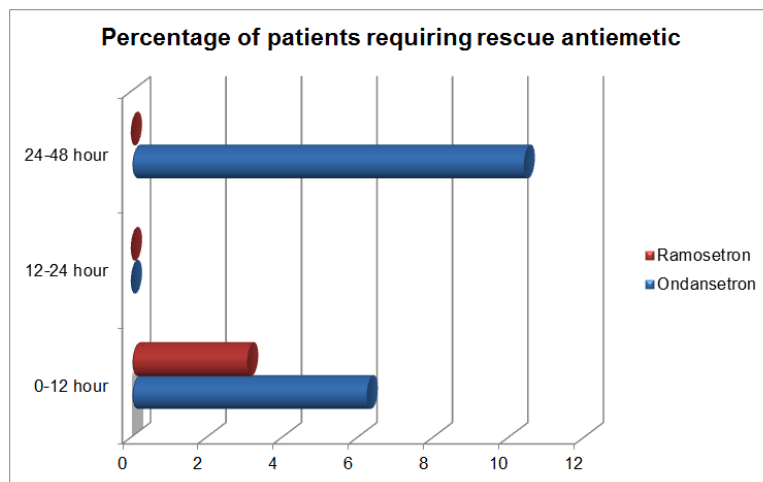


At 0-12 hr and 12-24 hr, the difference between ondansetron and ramosetron group in case of number of patients experiencing vomiting is statistically

insignificant, but there is statistically significant difference between Group A and Group B at 24-48 hour in case of patients having vomiting episodes.

Table-4: Patients requiring rescue antiemetic

	Group A		Group B		P value	Level of Significance
	Number	Percentage	Number	Percentage		
0-12 hour	3	6.25	1	2.08	0.3077	P > 0.05
12-24 hour	0	0.00	0	0.00	0.00	-
24-48 hour	5	10.41	0	0.00	0.0214	P < 0.05



At 0-12 hr and 12-24 hr, the difference between ondansetron and ramosetron group in case of number of patients requiring rescue antiemetic is statistically insignificant, but there is statistically significant difference between patients requiring rescue antiemetic in Group A and Group B at 24-48 hour, showing that group A (ondansetron) patients

required more rescue antiemetic in that time period than group B (ramosetron) patients.

DISCUSSION

Post Operative Nausea and Vomiting, defined as nausea and or vomiting occurring within 48h after surgery, is one of the most frequent complication

causing distress to patients and delaying post operative recovery [1]. The incidence of PONV after middle ear surgery without prophylactic antiemetic treatment is severe, frequent and prolonged [2]. Numerous studies have investigated about the prevention and treatment of PONV but the development of a single effective antiemetic therapy has been hampered due to its multifactorial nature involving anaesthetic, surgical, and individual risk factors specially in middle ear surgeries [12].

Etiology of PONV after middle ear surgeries is multifactorial, frequent and prolonged as it involves stimulation of the labyrinth [2]. There are abundant 5-HT₃ receptors present in the vicinity of the trigeminal nerve and vestibular labyrinth; hence, 5-HT₃ receptor antagonists are efficacious in middle ear surgeries. In addition 5-HT₃ antagonists prevent serotonin from binding to 5-HT₃ receptors on the ends of the vagus nerve's afferent branches, which send signals directly to the vomiting center in the medulla oblongata and in the chemoreceptor trigger zone of the brain. So 5HT₃ antagonists were aptly chosen for PONV prophylaxis in this study. Ondansetron, the most commonly used prophylactic 5-HT₃ antagonist [13] has been shown to be effective with minimal side effects in preventing PONV as a single dose of 4mg in intravenous route in multiple studies [14-16] when administered towards the end of the surgery [17]. Ramosetron, a new 5-HT₃ receptor antagonist, has higher potency and prolonged activity than previously developed 5-HT₃ antagonists as an antiemetic after chemotherapy [18]. Ramosetron in a dose of 0.3mg have been found to be very effective in preventing PONV in many surgeries and it is also advocated to be administered towards the end the of surgery [19, 9].

There have been multiple studies which evaluated and compared both these drugs in PONV prophylaxis in other surgeries like Jin Joo *et al.*, found Ramosetron (0.3mg) to be superior than Ondansetron (4mg) for PONV prophylaxis in strabismus surgery [20], Yiping Li *et al.*, in their metaanalysis for PONV prevention in laparoscopic surgeries found out that Ramosetron (0.3mg) was comparable to 8mg Ondansetron and superior to 4mg Ondansetron in intravenous route [21], Hahm TS found out that Ramosetron (0.3mg) was better than Ondansetron (4mg) in PONV prophylaxis in total knee replacement surgeries [18].

Sameer Desai *et al.*, in their study of comparison of the antiemetic effect of Ramosetron with the combination of Dexamethasone and Ondansetron in middle ear surgery in 2013 found out that the incidence of nausea was significantly lower in the Dexamethasone and Ondansetron group compared to the Ramosetron group between 2 and 24 hours [22]. However the present study was undertaken to evaluate and compare the commonly used, easily available drug Ondansetron

(Group A) with a newer, reportedly effective, but less commonly used drug Ramosetron (Group B) as a monotherapy in the prophylaxis of PONV in middle ear surgeries under general anaesthesia from 0 to 48 hrs post operatively.

Ondansetron (4mg) and Ramosetron (0.3mg) was given as a single intravenous injection, 10 min before extubation of patient after standard general anaesthesia for middle ear surgery. Evaluation and comparison was made between the vital parameters and antiemetic efficacy of prophylactic Ondansetron with Ramosetron from 0 to 48 hours post operatively.

This study was carried out with 48 patients in each group of either sex, weighing 50-70 Kg and age ranging between 18-60 years. Only those patients belonging to ASA physical status 1 and 2 were included in the study. According to the simplified risk score system of Apfel [23] there is higher risk of PONV in a patient of female gender, nonsmoking, the use of postoperative opioids, and with a prior history of motion sickness or PONV. The patients selected for this study were found to be comparable in distribution according to their sex. Instead of opioids, paracetamol infusion and Diclofenac injection have been used as post operative analgesia and patients having history of motion sickness and PONV were excluded from this study.

Sossai R, Johr M, Kistler W *et al.*, found out in his study "Postoperative vomiting in children-A persisting unsolved problem" that the incidence of PONV changes with age [24]. The mean age of patients in our study in Group A was 34.21 +/- 11.7 years and the mean age in Group B was 33.42 +/-10.4years. Both the groups were comparable in terms of age as difference between mean age of the 2 groups were found to be insignificant.

The duration of anaesthesia and surgery were similar in both the groups. Drug used during general anaesthesia were similar in both groups. The mean duration of anaesthesia in group A was 104.23 min, in group B it was 102.33 min. The mean duration of surgery in group A was 88.44 min and in group B it was 87.2 min. No statistically significant difference was noted between the two groups with respect to duration of anaesthesia and surgery duration.

It was found that there was no statistical significance between the two groups in terms of pulse rate, systolic and diastolic blood pressure, respiratory rate and the arterial oxygen saturation in the two groups. These findings were in correlation with other studies comparing prophylactic antiemetic efficacy between 5HT₃receptor antagonist drugs.

Anil Shetty *et al.*, in their research article studying the analogy and collation of intravenous ramosetron and ondansetron for prevention of nausea and vomiting in middle ear surgeries in a south Indian tertiary care hospital concluded that Ramosetron (0.3mg) was more efficacious and safer than Ondansetron (4mg) [11]. Alternatively, Yoon DG *et al.*, depicted that prophylactic therapy with Ramosetron (0.3mg) is as effective and safe as ondansetron for PONV in middle ear surgery under general anaesthesia with Sevoflurane and Remifentanyl [10].

However this present study found out that both Ramosetron and Ondansetron were effective in preventing PONV, Ramosetron was found to be more effective than Ondansetron (4mg) in numbers and percentages but the differences between both the groups were not statistically significant in preventing PONV in middle ear surgeries after general anaesthesia during the 0-24 hours post operative period, the difference between both the groups was statistically significant in the time period 24-48 hours. This shows that Ramosetron is significantly better in preventing emetic episodes (nausea, vomiting and both) in this time period compared with that of Ondansetron (Table 1, 2 & 3). In addition to this Ramosetron usage showed significant decrease in rescue antiemetic requirement than Ondansetron in the 24 to 48 hours post operative period (Table-4). Hence it can be suggested that ramosetron is a more potent and effective and longer acting antiemetic agent compared to Ondansetron in preventing PONV in middle ear surgeries under general anaesthesia.

CONCLUSION

In conclusion, it was found that Ondansetron and Ramosetron showed comparable efficacy in preventing PONV upto 24hours postoperatively in middle ear surgery patients. However prophylactic administration of single dose IV Ramosetron (0.3 mg) has significantly better efficacy than single dose IV Ondansetron (4 mg) in reducing the incidence of PONV and requirement of rescue analgesic over the 24 to 48-hours postoperative period in patients undergoing middle ear surgery under general anaesthesia. The limitation of this study was that we compared the efficacy of Ramosetron and Ondansetron by their known usual effective and manufacturer recommended doses (0.3 mg and 4mg respectively) because their equipotent doses were unknown at the time of study commencement. Further studies are needed to investigate the equipotency of ramosetron and ondansetron to prevent PONV. Also, a larger study with large sample size needs to be conducted to establish the author's point of view with solidarity.

ABBREVIATION

PONV - Post Operative Nausea and Vomiting
IV - Intravenous

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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