Original Article

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# Comparison of Ramosetron and Palonosetron for Control of Post-operative Nausea and Vomiting following Middle Ear Surgeries: A Prospective Randomized Double-blind Study

**Pallavi Ahluwalia[1], Amit Ahluwalia[2], Fauzia Rehman[3], Anka Sagar[3], Rakesh Kumar[3]**

[1]Associate Professor, Department of Anaesthesia, Teerthanker Mahaveer Medical College, Moradabad, Uttar Pradesh, India, [2]Consultant Orthopaedics, Vivekanand Hospital and Research Centre, Moradabad, Uttar Pradesh, India, [3]Assistant Professor, Department of Anesthesia, Teerthanker Mahaveer Medical College, Moradabad, Uttar Pradesh, India

## Abstract

**Background:** Post-operative nausea vomiting (PONV) is a distressing complaint particularly in high-risk patients. 5-HT3 receptor antagonists has proved a promising role in the prophylaxis of PONV.

**Aim:** We aim to compare the anti-emetic responsiveness of ramosetron and palonosetron in post-operative patients of middle ear surgeries.

**Materials and Methods:** In the present randomized, prospective double-blind study is including 60 American Society of Anesthesiology Grade I/II female patients, between 25 and 40 years of age undergoing elective middle ear surgeries. Patients were divided into two groups; Group R: Injection ramosetron 0.3 mg (intravenous [IV]) in 2 ml solution and Group P: Injection palonosetron 0.075 mg (IV) made 2 ml after adding 0.5 ml normal saline, were administered for prevention of PONV in the present study. The study drugs were administered before shifting of the patient from the operating room to the post anesthesia care unit. The efficacy, as well as side effects of ramosetron and palonosetron was documented and compared.

**Results:** In the present study, the complete response was observed in 90.91% and 70.91% of the patients observed during 0-2 h and 2-24 h respectively in Group R while in Group P no PONV was found in 92.73% and 80% of the patients within the same time frame ($P > 0.05$). However, during 24-48 h significant complete response was observed among both the groups ($P = 0.03$). Severity of nausea, retching and vomiting was also found to be significantly high in ramosetron group as compared to the patients received palonosetron. Total rescue antiemetic was given more among ramosetron group. However, no significant difference was observed when compared with palonosetron group ($P = 0.11$).

**Conclusion:** Palonosetron was found an effective and better antiemetic than ramosetron in patients undergoing middle ear surgeries.

**Key words:** Palonosetron, Post-operative nausea vomiting, Ramosetron, Serotonin 5-HT3 receptor antagonists

## INTRODUCTION

Post-operative nausea and vomiting (PONV) is a common complaint among the patients of middle ear surgeries with a reported incidence of 62-80%.[1-3] PONV at times is more distressing than post-operative pain and can further 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.[4] Middle ear surgeries stimulate the vestibular system thereby increases the incidence of nausea and vomiting.[5] The introduction of 5-HT3 antagonists in medical era is a milestone for promoting day care surgery and anesthesia. These drugs are very commonly used now a days, with more safety and favorable side-effects profile

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**Corresponding Author:** Dr. Pallavi Ahluwalia, Department of Anaesthesia, Teerthankar Mahaveer Medical College, Delhi Road, Moradabad - 244 001, Uttar Pradesh, India. Phone: +91-7599111465. E-mail: drpallaviahluwalia@yahoo.com

as they lack the extra-pyramidal, dysphoric, sedative and side effects of other commonly used antiemetics.

Ondansetron is the most favored drug among the medical professionals and is being routinely used either alone or in combination with other drugs, for the prophylaxis of PONV in day care surgery. A newer drug, ramosetron, is a recently developed selective 5-HT3 receptor antagonist. It exhibits significantly greater 5-HT3 receptor binding affinity with slow dissociation rate thus implying better potency and longer receptor antagonizing effects compared with Ondansetron.[6] Thereafter, palonosetron ("second-generation" 5-HT3 receptor antagonist with a mean elimination half-life of about 40 h) is introduced possessing the property of even better receptor-binding affinity than the "first generation" 5-HT3 antagonists.[7,8] Moreover, it also have a property to bind to the receptor at an allosteric site different from those that bind ondansetron and granisetron.[7]

Extensive Medline search revealed a number of studies comparing the efficacy of ramosetron and palonosetron on PONV, but controversy still persists regarding the best suitability of the drug for day care anesthesia. Moreover, lack of comparative studies between these two drugs in developing countries and limited availability of literature regarding the use of these drugs for middle ear surgeries compelled us to perform our study. Therefore, we designed a prospective randomized study to compare the efficacy of ramosetron and palonosetron in preventing PONV for the patients undergoing middle ear surgeries.

## MATERIALS AND METHODS

After approval from the Institutional Ethical Committee and written informed consent, we conducted a study including 60 American Society of Anesthesiology Grade I/II female patients, between 25 and 40 years of age undergoing elective middle ear surgeries in Teerthankar Mahaveer Medical College from November 2014 to April 2015. Patients with history of drug abuse, body mass index >35, patients on chronic steroid therapy, and patients with diabetes mellitus or cardiovascular disease, history of motion sickness, gastrointestinal disease was excluded from the study.

A consultant anesthesiologist assessed all patients during pre-anesthetic evaluation and alprazolam (0.5 mg) orally was prescribed in all patients on the night before surgery and advised nil per orally from midnight. Before reaching the operating room (OR) a good intravenous (IV) access was secured with 20 G cannula and preloading was done with 10 ml/kg of ringer lactate solution. Monitoring devices for ECG, heart rate, oxygen saturation and end-tidal carbon dioxide were attached.

Randomisation was performed by computer generated program and the patients were allocated in two groups of 55 patients each. Group R: Injection ramosetron 0.3 mg (IV) in 2 ml solution and Group P: Injection palonosetron 0.075 mg (IV) made 2 ml after adding 0.5 ml normal saline, were administered for prevention of PONV in the present study. Drugs were prepared by a blinded anesthesia technician not involved in the study in identical 5 ml syringes and were administered according to the randomization list.

A well-defined anesthesia regimen was used in all the patients that included induction with injection propofol 2 mg/kg (IV) and injection fentanyl 1 μg/kg (IV). Intubation was facilitated by using injection vecuronium 0.1 mg/kg (IV). After confirming correct placement of endotracheal tube by capnography, we secured a nasogastric tube. Maintenance of anesthesia was done using nitrous oxide (66%) and isoflurane (1-2%) in oxygen. Intra-operative muscle relaxation was maintained with intermittent doses of injection vecuronium. At the end of the surgery, injection diclofenac 75 mg (intramuscular) was given and reversal of neuromuscular blockade was performed with injection neostigmine 0.05 mg/kg (IV) and Injection glycopyrrolate 0 1 mg/kg (IV). After thoroughly doing the oral/nasogastric suction, patients were extubated in a fully awake state. Ramosetron 0.3 mg or palonosetron 0.075 mg was administered IV before shifting of the patient from the OR to the post-anesthesia care unit (PACU). No opioids were given for post-operative analgesia at any point of time. In the PACU, patients were monitored for nausea, retching, vomiting, pain, vital signs, and post-anesthetic discharge score. Patients were closely monitored for 48 h and any complaint of nausea, retching, and vomiting or adverse drug effect was recorded by an independent observer who was blinded to the study.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit whereas retching was defined as the labored spasmodic, rhythmic contraction of the abdominal muscles without expulsion of gastric contents, and vomiting was defined as the forceful expulsion of gastric contents from the mouth.[9-11] Rescue antiemetic (not belonging to the 5-HT3 receptor antagonist group, i.e. metoclopramide 10 mg) was given if two or more episodes of emesis occurred in each observation period. We made no distinction between vomiting and retching for treatment purpose. A trained nurse taking care of the patient and blinded to the study recorded all episodes of PONV (nausea, retching, and vomiting) either by direct questioning or by spontaneous complaint by the patients during three periods within the first 48 h after anesthesia: 0-2 h in the PACU, 2-24 h in the general ward and 24-48 h also in the general ward. Nausea was scored

on an 11-point verbal rating scale from 0 (no nausea) to 10 (worst possible nausea): Severity was scored as mild (1-3), moderate (4-6), or severe (7-10).[12] Any side effects/adverse effects were recorded during the study period by the attending anesthesiologist and otolaryngorhinologist. Patient satisfaction regarding their satisfaction to be free of nausea and vomiting was performed on a four-point Likert scale (dissatisfied, neutral, satisfied, and highly satisfied) at the completion of the study.[8]

### Statistical Analysis

Sample size was predetermined using a power analysis to achieve an 80% chance (b = 0.2) of detecting a 40% reduction in PONV from a basal incidence of 70% (from 70% to 42%) with an assumed significance level of a = 0.05.[13] A minimum number of 49 patients in each group were calculated and considering 10% attrition rate we included 55 patients in each group. Data analysis was performed using SPSS, version 19 (SPSS Inc., USA). All the statistical tests were two-tailed. All the values were expressed as mean ± standard deviation. A $P < 0.05$ was considered as significant.

## RESULTS

All patients were successfully enrolled and underwent middle ear surgery in our study without any dropouts. The ramosetron group and the palonosetron group were comparable with respect to patient's demographic data, duration of surgery/anesthesia (Table 1).

The complete response was observed in 90.91% and 70.91% of the patients during 0-2 h and 2-24 h respectively in Group R while in Group P no PONV was found in 92.73% and 80% of the patients within the same time frame ($P > 0.05$) (Table 2). However, during 24-48 h significant complete response was observed among both the groups ($P = 0.03$). Nausea severity was more in Group R as compared to Group P, and significant difference was observed during 2-24 h ($P = 0.05$) and 24-48 h ($P = 0.01$). Episodes of retching was also found to be significant during 2-24 h and 24-48 h among Group R (14.55% and 27.28%) as compared to Group P (3.63% and 7.28%) ($P = 0.04$ and 0.001). During first 24 h frequency of vomiting was comparable among the two groups. However, during 24-48 h we observed significant increase in the episodes of vomiting in Group R ($P = 0.04$) (Table 2). Total rescue antiemetic was given more among ramosetron group, however no significant difference was observed when compared with palonosetron group ($P = 0.11$). On enquiry with the patients 17 patients advocated satisfaction with ramosetron while 24 patients were satisfied with palonosetron ($P = 0.20$) (Table 2).

Transient dizziness, dyspepsia, headache, weakness and flushing/erythema were noted in 1, 2, 4, 4, and 5 patients, respectively, in Group R, while the same was observed in 1, 1, 5, 1, and 3 patients in Group P (Table 3). The flushing/erythema at the site of injection was non-tender that subsided on its own without requiring any treatment over the next 24 h (Table 3).

## DISCUSSION

In middle ear surgeries, continuous drilling and irrigating the bone causes vestibular stimulation leading to a distressing problem of PONV.[14] The incidence of PONV after general anesthesia is 20-30% and it becomes more

**Table 1: Demographic variables (mean±SD)**

| Characteristics | Group R | Group P | *P* value |
|---|---|---|---|
| Age (years) | 29.82±4.62 | 28.87±3.74 | 0.23 |
| Height (cm) | 153.64±3.51 | 154.27±2.87 | 0.30 |
| Weight (kg) | 53.65±4.47 | 54.52±5.21 | 0.35 |
| Duration of surgery (min) | 126.75±7.92 | 129.54±8.89 | 0.10 |
| Duration of anesthesia (min) | 131.61±8.64 | 133.62±9.83 | 0.26 |

SD: Standard deviation

**Table 2: Comparison of frequency of nausea, retching and vomiting episodes in patients administered ramosetron and palonosetron**

| Variables | Groups | Events frequency (*n* (%)) | | |
|---|---|---|---|---|
| | | 0-2 h | 2-24 h | 24-48 h |
| Complete response | Group R | 50 (90.91) | 39 (70.91) | 29 (52.73) |
| | Group P | 51 (92.73) | 44 (80.00) | 40 (72.73) |
| | *P* value | 0.72 | 0.26 | 0.03* |
| Nausea severity (mild, moderate, severe) | Group R | 1/2/1 | 4/9/6 | 5/8/7 |
| | Group P | 1/1/1 | 2/4/4 | 3/4/2 |
| | *P* value | 0.69 | 0.05* | 0.01* |
| Retching | Group R | 3 (5.46) | 8 (14.55) | 15 (27.28) |
| | Group P | 1 (1.81) | 2 (3.63) | 4 (7.28) |
| | *P* value | 0.3 | 0.04* | 0.001* |
| Vomiting | Group R | 4 (7.28) | 11 (20.00) | 17 (30.91) |
| | Group P | 3 (5.46) | 6 (10.91) | 8 (14.55) |
| | *P* value | 0.69 | 0.18 | 0.04* |
| Total rescue antiemetic given (no. of patients) | Group R | 25 (45.46) | | |
| | Group P | 17 (30.91) | | |
| | *P* value | 0.11 | | |
| Overall satisfaction (dissatisfied/neutral/ satisfied/highly satisfied) | Group R | 28/10/10/7 | | |
| | Group P | 19/12/16/8 | | |
| | *P* value | 0.20 | | |

*$P<0.05$

**Table 3: Adverse events in number (percentage)**

| Adverse event | Group R | Group P |
|---|---|---|
| Dizziness | 1 (1.81) | 1 (1.81) |
| Dyspepsia | 2 (3.63) | 1 (1.81) |
| Headache | 4 (7.28) | 5 (5.46) |
| Weakness | 4 (7.28) | 1 (1.81) |
| Flushing | 5 (5.46) | 3 (7.28) |

worrisome after gynecologic, laparoscopic, breast and middle ear surgeries.[15]

Many consensus guidelines were proposed in the past to eliminate the problem of PONV. The recent introduction of palonosetron together with its greater 5-HT3 receptor binding appealed many researchers to choose this drug in their studies. Bicer *et al.*[16] performed a study to compare different doses (0.5, 1.0, and 1.5μg/kg) of palonosetron in pediatric patients undergoing strabismus surgery and recommended further evaluation as all appeared effective doses. However, FDA has now established that the minimum effective dose of palonosetron for the prevention of PONV is 0.075 mg.[17,18] Hence, we choose the same dose of palonosetron for our study.

The complete response (patients with no PONV) was seen more in the patients given palonosetron than ramosetron group, although the results were comparable among them during 0-2 h and 2-24 h' time period. However, after 24-48 h postoperatively 52.73% of the patients of Group R had complete response whereas 72.73% of the patients did not complain of PONV of Group P ($P = 0.03$). The better outcome after 24 h shown by the patients given palonosetron might be because of the greater half-life of palonosetron (40h) as compared to patients received ramosetron. This is similar to various studies that the palonosetron was observed as better long duration effect than ramosetron.[12,19,20] In a comparative study done by Fujii *et al.*,[21] they observed a complete response in 90% of the patients in ramosetron group while 86% in patients who were given Granisetron. During 24-48 h after surgery, a complete response was observed in ramosetron and Granisetron group as 90 and 66%, respectively. Oshima *et al.*[22] found that 30 mg of Tandospirone imparted a complete response in 67% of the patients. Various researchers also observed similar effectiveness of ramosetron in their studies during the first 24 h postoperatively, although they compared the drug with Ondansetron.[6,23]

The patients received ramosetron experienced more severe grade of nausea than those of patients given palonosetron from 2 to 48 h. Chattopadhyay and Goswami[19] supports our study in which they also observed that severity of nausea was statistically significant with ramosetron group within 2-48 h postoperatively. In high-risk patients, after thyroidectomy palonosetron proved to be more effective than ondansetron especially 2-24 h after surgery.[14]

We have also included the episodes of retching in our study in which the effectiveness of palonosetron is evident as the patients received ramosetron suffered from more episodes of retching 2 h postoperatively. Such findings are not observed by most of the researchers of PONV in their studies.

In terms of vomiting, although more number of patients experienced vomiting in ramosetron group but significant difference was not observed during the first 24 h. Due to better receptor binding to an allosteric site and slow dissociation property of palonosetron receiving patients, the episodes of vomiting rises significantly in ramosetron group 24-48 h after surgery. As the episodes of vomiting are higher in ramosetron group, therefore, the requirement of rescue emetic is more in Group R than Group P ($P = 0.11$). The persistent beneficial effect of palonosetron as compared to ramosetron could be explained from the fact that the former drug has a prolonged elimination half-life.[8] So, palonosetron is a better effective alternative than ramosetron after first post-operative day.

Upon enquiring the patient satisfaction score by Likert scale, palonosetron better fulfilled the satisfaction score than ramosetron and it can be explained by the fact that during our study better results are observed with Group P patients than Group R.

In the present study, a significant number of adverse effects was also noted among both the groups. However, all adverse effects were uneventful and successfully managed.

Another possible mechanism for PONV could be the use of Nitrous oxide during intra-operative period. We have used Nitrous oxide in our cases due to financial constraints of our hospital. However, use of short-acting opioid or a continuous propofol infusion might be a better option.[24-26]

### Limitations

In the present study, a control group should be there whereby we can observe PONV at a basal level but post-operative patients of middle ear surgery is itself prone to higher chances of PONV and in such situation giving them a placebo would be injustice and unethical to those patients. Secondly, ramosetron has a short half-life than palonosetron and in such circumstances the dosing schedule for ramosetron should be multi-regimen but including more dosing schedules of ramosetron would lead to bias in the study. Thirdly, we have given Fentanyl during induction of anesthesia, being an opioid it can exaggerate PONV. However, in recent study it is observed that pain treated with opioids actually prevents PONV.

## CONCLUSION

The present study clearly states that palonosetron is a better and effective alternative for PONV in middle ear surgeries during the first and second post-operative day. A good patient's satisfaction and a prolong duration of anti-emetic cover advocates its use in patients undergoing middle ear surgeries in general anesthesia.

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