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## A comparative clinical study of methylprednisolone with ondansetron versus methylprednisolone with ramosetron in preventing postoperative nausea and vomiting in patients undergoing middle ear surgeries

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### Abstract

**Background:** Postoperative nausea and vomiting (PONV) is one of the most unpleasant complications of anaesthesia and is more common following middle ear surgeries. Ondansetron, a 5-HT<sub>3</sub> (5-hydroxytryptamine type 3) receptor antagonist provides significant reduction in early PONV. The other 5-HT<sub>3</sub> antagonist ramosetron, with long duration of action, has been found to be more effective than ondansetron in reducing the early as well as delayed PONV. The antiemetic effects of glucocorticoids (dexamethasone and methylprednisolone) are well documented. So, the present study was designed to compare the efficacy of the combination of intravenous methylprednisolone and ondansetron with combination of intravenous methylprednisolone and ramosetron in preventing postoperative nausea and vomiting in patients undergoing middle ear surgeries.

**Methods:** Sixty patients in the age group of 18-60 years, with American Society of Anaesthesiologists (ASA) physical status classification I or II, undergoing middle ear surgery were randomly allocated to receive a combination of methylprednisolone 40 mg (given at the beginning of surgery) and ondansetron 4 mg (given near the end of surgery) (group MO, n=30) or combination of intravenous methylprednisolone 40 mg and ramosetron 0.3 mg (near the end of surgery) (group R, n=30), by a computer-generated randomization table. Incidence of PONV in the both groups were studied and compared.

**Results:** There was no significant difference in PONV between the groups in the first 2 h after the surgery. Between 2 and 24 h, the incidence of nausea was significantly lower in the methylprednisolone and ondansetron group compared to the methylprednisolone and ramosetron group (P=0.01). Between 24 and 48 h, there was no difference between the two groups with respect to incidence of nausea and vomiting.

**Conclusion:** The combination of methylprednisolone and ondansetron is superior to combination of methylprednisolone and ramosetron for prevention of PONV after middle ear surgery especially in treatment of early PONV. Therefore, we recommend combination of methylprednisolone and ondansetron for prophylaxis for PONV in middle ear surgeries.

**Keywords:** postoperative nausea and vomiting; methylprednisolone, ondansetron, ramosetron

### Introduction

Postoperative nausea and vomiting (PONV) is one of the most unpleasant complications of anaesthesia and is more common following middle ear surgeries. It can lead to medical complications, unanticipated admissions and prolonged stay in the post anaesthesia care unit [1, 2, 3]. Pain and postoperative nausea and vomiting can be very distressing for the patient and may delay oral intake.

Ondansetron, a 5-HT<sub>3</sub> (5-hydroxytryptamine type 3) receptor antagonist provides significant reduction in early PONV [4]. It is an effective drug for both prophylaxis and treatment of PONV. Ondansetron was considered to be the first universally effective antiemetic for PONV, and it was later found to have less anti-nausea and more anti-vomiting efficacy [5].

The newer 5-HT<sub>3</sub> antagonist ramosetron, with long duration of action, has been found to be more effective than ondansetron in reducing the early as well as delayed PONV, when used in other surgeries [6].

The antiemetic effects of glucocorticoids (dexamethasone and methylprednisolone) are well documented; however, their mechanism is poorly understood. Dexamethasone was traditionally used to prevent nausea and vomiting following chemotherapy.

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Presently dexamethasone is also used in the prevention of post-operative nausea and vomiting [7]. Similarly methylprednisolone has also proved to be effective in prevention of chemotherapy induced emesis [8,9].

Ondansetron was useful mainly in the prevention of early PONV [9], and dexamethasone and methylprednisolone were mainly useful in the prevention of late PONV [12]. Their combination was found to be superior in the prevention of PONV following middle ear surgeries [2,3].

So, the present study was designed to compare the efficacy of the combination of intravenous methylprednisolone and ondansetron with the combination of intravenous methylprednisolone and ramosterone in preventing postoperative nausea and vomiting in patients undergoing middle ear surgeries.

## Methods

After obtaining the ethical committee approval of our hospital, a written informed consent was obtained from all the patients for this prospective, randomized, double-blind study. Sixty patients in the age group of 18-60 years, with American Society of Anaesthesiologists (ASA) physical status classification I or II, undergoing middle ear surgery in our medical college hospital were included in the study. The patients who had received other antiemetic medication or perioperative steroids for any reason were excluded from the study. The presence of other risk factors for PONV such as history of smoking, history of motion sickness was noted. Tablet diazepam (10 mg, PO) was given as premedication the night before and on the morning of the surgery for anxiolysis. General anaesthesia was induced with fentanyl (2-3 mcg/kg), propofol (2 mg/kg), and vecuronium (0.1 mg/kg) to facilitate endotracheal intubation. Anaesthesia was maintained with sevoflurane 2%-2.5% with nitrous oxide 60% in oxygen. The patients received intravenous diclofenac 75 mg infusion during the surgery. Ventilation was mechanically controlled and adjusted to maintain an end-tidal concentration of CO<sub>2</sub> between 35 and 40 mmHg. The patients' heart rate, mean arterial pressure, and minimum anaesthetic concentration (MAC) were noted every 30 min during surgery. Neuromuscular block was reversed with neostigmine and glycopyrrolate at the end of surgery. The total amount of reversal used in millilitres was noted (1 ml=neostigmine 0.5 mg and glycopyrrolate 0.1 mg). After the clinical assessment of adequacy of the reversal of neuromuscular block, trachea was extubated. Near the end of surgery, all the patients were given morphine 0.1 mg/kg intravenously for the postoperative analgesia. Patients were randomly allocated to receive either combination of methylprednisolone 40 mg (given at the beginning of surgery) and ondansetron 4 mg (given near the end of surgery) (group MO, n=30) or combination of methylprednisolone 40 mg (given at the beginning of surgery) and ramosetron 0.3 mg (near the end of surgery) (group MR, n=30), by a computer-generated randomization table. Primary efficacy variables assessed were the incidence and severity of nausea and the incidence of vomiting in the first 48 h after the surgery. Secondary efficacy variables included the use of additional antiemetic as rescue, pain intensity, and medication-associated complications. These variables were assessed by an

investigator who was blinded to the treatment group. Evaluations were performed in the first 2 h, 2-24 h, and 24-48 h postoperatively. Nausea was defined as a subjectively unpleasant sensation associated with the urge to vomit. Vomiting was defined as the forceful expulsion of gastric contents. The severity of nausea was graded as: 0=none, 1=mild, 2=moderate, and 3=severe. The severity of postoperative pain was assessed by using a visual analog scale (VAS) that ranged from 0 (no pain) to 10 (worst pain imaginable). If the patient developed nausea or vomiting in the postoperative period, then prochlorperazine 25 mg was given slowly intravenously as rescue antiemetic. If the patient's PONV persisted despite administering rescue antiemetic, the physician was allowed to give dexamethasone or ondansetron or any other antiemetic as per their discretion. All the patients received diclofenac tablets three times a day for the postoperative pain. If they complained of pain  $\geq 5$  on VAS, pethidine was used as a breakthrough analgesic. The patients were enquired about the common side effects of medication, namely, headache, dizziness, drowsiness, constipation, and flushing.

Statistical analyses were performed using SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the chi-square test or fisher's exact test. Continuous variables were compared using independent t-test. Data are presented as mean  $\pm$  standard deviation or as the number of patients and percentages. P value of less than 0.05 was considered statistically significant.

## Results

All the sixty patients completed the study protocol (no dropouts) and were analyzed for primary efficacy. The patient's characteristics, duration of surgery or anaesthesia, incidence of motion sickness or history of PONV, and nonsmoking status were not significant between the two groups. The calculated simplified risk score of Apfel was also comparable between the groups [Table 1]. There was no significant difference in the measured mean arterial pressure, heart rate, and MAC values between the groups. There was no significant difference in PONV in the first 2 h after the surgery. Between 2 and 24 h, the incidence of nausea was significantly lower in the methylprednisolone and ondansetron group compared to the methylprednisolone and ramosetron group (P=0.021). The incidence of vomiting and use of rescue antiemetic was not different between the groups. The patients who never developed nausea or vomiting were considered to have had complete response. The incidence of vomiting and use of rescue antiemetic was not different between the groups. The patients who never developed nausea or vomiting were considered to have had complete response. Between 2 and 24 h, higher number of patients in the methylprednisolone and ondansetron group had a complete response compared to the methylprednisolone and ramosetron group (81% vs. 63%). Between 24 and 48 h, the incidence of nausea and vomiting was more less in both the groups (93% vs. 95%). Overall, higher number of patients had a complete response in the methylprednisolone and ondansetron group compared to ramosetron group (71% vs. 40%) [Table 2]. Incidences of side effects were not different between the groups. There was no significant difference in the pain scores between the groups [Table 3].

**Table 1:** Patient characteristics, surgery and anaesthetic data

	Group MO	Group MR	P value
n	30	30	
Age (years)	31±3.5	29±2.9	0.08
Weight (kg)	56±4.8	58±2.6	0.07
Sex, M/F	18/12	20/10	0.35
Nonsmoker	23	21	0.29
History of motion sickness or history PONV	04	05	0.06
Anaesthesia duration (min)	204±1.5	199±2.6	0.45
Duration of surgery (min)	188±5.4	187±2.4	0.34
Dose of morphine (mg)	5.5±0.4	5.7±0.6	0.09
Ossiculoplasty	4	5	0.11

**Table 2:** Incidence and severity of nausea and vomiting and requirements for rescue antiemetic treatment

	Group MO	Group MR	P value
<b>First 2 h</b>			
Nausea: Mild/moderate/severe	1/3/2	1/4/2	0.12
Vomiting	5	6	0.23
Rescue antiemetic	5	6	0.23
No PONV	24	23	0.32
<b>First 2-24 h</b>			
Nausea: Mild/moderate/severe	1/3/3	3/7/5	0.031
Vomiting	5	7	0.23
Rescue antiemetic	5	7	0.23
No PONV	23	15	0.036
<b>First 24-48 h</b>			
Nausea: Mild/moderate/severe	0/3/4	6/7/6	0.014
Vomiting	4	8	0.018
Rescue antiemetic	4	8	0.018
No PONV	24	11	0.021
No PONV in 48 h	23	11	0.032
<b>Side effects</b>			
Headache	3	4	0.15
Dizziness	2	3	0.21

**Table 3:** Pain scores

	Group MO	Group MR	P value
VAS score in the first 2 h	1.8±1.0	2.0±1.1	0.43
VAS score in 2-24 h	2.7±0.9	2.8±0.8	0.32
VAS score in 24-48 h	2.9±1.3	3.0±1.1	0/40

**Discussion**

PONV is one of the common problems encountered after middle ear surgeries, with an incidence up to 80%, when no antiemetics are used [1]. The cause of PONV after middle ear surgeries is multifactorial. There are abundant 5-HT<sub>3</sub> receptors present in the vicinity of trigeminal nerve and vestibular labyrinth; hence, 5-HT<sub>3</sub> receptor antagonists are efficacious in middle ear surgeries. The 5-HT<sub>3</sub> antagonists like ondansetron has been proved to be an efficacious antiemetic in decreasing the incidence PONV after middle ear surgery [2]. Ondansetron has been shown to be more effective in prevention of early but not late PONV due to the shorter duration of action of ondansetron (4 h), whereas corticosteroids have shown to have more evident action in the prevention of late PONV [3, 5]. Corticosteroids have been proposed to act as antiemetic by serotonin inhibition in the gut through prostaglandin antagonism, and also by significant reduction in the tissue inflammation, thus leading to reduction in the ascending impulse to the vomiting center. Corticosteroids have also been found to improve the action of other antiemetic drugs by sensitizing the pharmacologic receptors to these antiemetics [17]. Therefore, the combinations of corticosteroids and 5-HT<sub>3</sub> antagonist have

an additive effect in reducing the PONV. Thus, the combination of ondansetron and methylprednisolone can decrease the incidence of both early and late nausea and vomiting. Due to the stimulation of the labyrinth, PONV continues for longer duration in middle ear surgeries. So use of combination of ondansetron and methylprednisolone for prevention of PONV than using ondansetron alone. Ramosetron is a relatively newer 5-HT<sub>3</sub> receptor antagonist which is proposed to be more potent and a longer duration of antiemetic action than the ondansetron. This has been attributed to its higher binding affinity and slower rate of dissociation from the target receptor compared to ondansetron. The elimination half-life of ramosetron is also longer than that of ondansetron (9 h vs. 3.5 h) [10]. We noted that the combination of two antiemetics, ondansetron and methylprednisolone, had better efficacy than ramosetron and methylprednisolone when used as a prophylaxis against PONV especially in the first 24 hours. The results of our study is comparable to inference drawn in other meta-analyses [15, 16]. It is advocated that the drugs with different mechanisms of action should be used in combination to optimize the efficacy. The results of our study may be applicable to all the surgeries with expected long duration of nausea and vomiting. In this study, we noted that significantly more patients were free of PONV in the methylprednisolone and ondansetron combination group than the patients receiving monotherapy with ramosetron. Thus, the combination of methylprednisolone and ondansetron is superior to methylprednisolone and ramosetron for prevention of PONV after middle ear surgery. Therefore, we recommend combination of methylprednisolone and ondansetron for prophylaxis for PONV in middle ear surgeries.

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