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Original research article

Comparative study of methylprednisolone-palonosetron versus granisetron-methylprednisolone combination for prevention of post-operative nausea vomiting in middle ear surgeries

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Abstract

The incidence of post-operative nausea and vomiting (PONV) in middle ear surgeries ranges from 60% to 80%, in the absence of any antiemetic treatment. Glucocorticoids exert antiemetic properties by antagonizing prostaglandins or releasing endorphins. Present study was designed to compare the efficacy of the combination of intravenous (iv) methylprednisolone and palonosetron with the combination of iv methylprednisolone and granisetron in preventing PONV in patients undergoing middle ear surgeries. Present study was prospective, randomized, double-blind study, conducted in patients of either gender, of 18-60 years age group, with American Society of Anaesthesiologists (ASA) physical status classification I or II, undergoing middle ear surgery. Patients were randomly allocated to group MP (methylprednisolone and palonosetron) or group MG (methylprednisolone and granisetron) with 30 patients in each group.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 MP group compared to the MG group. Between 2-24 h, higher number of patients in the MP group had a complete response compared to the MG group [70% vs 43.3%].Overall, higher number of patients had a complete response in the methylprednisolone and palonosetron group compared to granisetron group (87% vs. 44%). There was no significant difference in the pain scores between the groups. Combination of methylprednisolone and palonosetron is superior to methylprednisolone and granisetron for prevention of PONV after middle ear surgery.

Keywords: Methylprednisolone, palonosetron, granisetron, post-operative nausea vomiting, middle ear surgeries

Introduction

Postoperative nausea and vomiting (PONV) is one of the most unpleasant complications of anaesthesia following middle ear surgeries. It can lead to medical complications, unanticipated admissions and prolonged stay in the post anaesthesia care unit[1,2]. The incidence of PONV in middle ear surgeries ranges from 60% to 80%, in the absence of any antiemetic treatment[3].

Nowadays, 5-HT3 (5-hydroxytryptamine 3) receptor antagonists are the first choice in laparoscopic, gynaecologic, middle ear surgeries because of its effectiveness, safety, and favourable side-effect profile as it lacks the sedative, dysphoric and extrapyramidal side effects of other drugs [4,5]. 5-HT3 receptor antagonists are widely used for preventing PONV. They selectively bind to 5-HT3 receptors in chemoreceptors within the brain and visceral vagal afferents [6].

Palonosetron, a second generation 5-HT3 receptor antagonists, with its distinct pharmacological features

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of greater binding affinity, longer half-life and eliciting 5-HT3 receptor internalization results in extended inhibition of receptor thereby preventing PONV for an extended period [7]. Granisetron, is a 5-HT3 antagonist, with stronger 5HT3 binding, is more potent and a longer acting antiemetic agent compared to ondansetronagainstemesisassociatedwith chemotherapy with less side effects[8].
Glucocorticoids exert antiemetic properties by antagonizing prostaglandins or releasing endorphins [9]. They can also potentiate other antiemetics by sensitizing pharmacologic receptors. Given these pharmacologic profiles, combining palonosetron and dexamethasone provides better prevention against chemotherapy-induced nausea and vomiting than palonosetron alone [10]. Methylprednisolone has also proved to be effective in prevention of chemotherapy induced emesis[11].
Present study was designed to compare the efficacy of the combination of iv methylprednisolone and palonosetron with the combination of iv methylprednisolone and granisetron in preventing PONV in patients undergoing middle ear surgeries.

Material and Methods
Present study was prospective, randomized, double-blind study, conducted in department of Anaesthesiology with help of department of ENT, at GMC Doda and GMC Kathua. Study duration was of 1 year (July 2019 to June 2020). Ethical committee approval of our hospital was taken for present study.

Inclusion criteria
Patients of either gender, of 18-60 years age group, with ASA physical status classification I or II, undergoing middle ear surgery, willing to participate in study.

Exclusion criteria
- Patients with known sensitivity to the study drugs.
- Patients with history of use of other antiemetic drug.
- Patients with motion sickness, central and/or nervous system disorders, cardiovascular, history of psychiatric illness.
- Pregnant and lactating women.
- Patients who had received other antiemetic medications for any reason.

Study was explained to patients and a written informed consent was obtained from all the patients. History, complaints, clinical examination findings were noted. The presence of other risk factors for PONV such as history of smoking, history of motion sickness was noted. After preanaesthetic fitness, patients were posted for surgery.
Patients were randomly allocated to group MP or group MG with 30 patients in each group, by a computer-generated randomization table.
- Group MP-received combination of methylprednisolone 40 mg (given at the beginning of surgery) and palonosetron 0.075 mg (given near the end of surgery).
- Group MG-received combination of methylprednisolone 40 mg (given at the beginning of surgery) and granisetron 1.0 mg (near the end of surgery).

Patients were induced with fentanyl (2 mcg/kg), propofol (2 mg/kg), and vecuronium (0.1 mg/kg) to facilitate endotracheal intubation. Anaesthesia was maintained with isoflurane 0.2-1.2% with nitrous oxide 60% in oxygen. The patients received iv paracetamol infusion 1 gm during the surgery. The patients heart rate, mean arterial pressure and oxygen saturation were noted throughout during surgery. Neuromuscular block was reversed with neostigmine and glycopyrrolate at the end of surgery. After the clinical assessment of adequacy of the reversal of neuromuscular block, patient was extubated.
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. 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 was =none, 1=mild, 2=moderate, and 3=severe.
- The severity of postoperative pain was assessed by using a visual analog scale (VAS) that ranged

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from 0 (no pain) to 10 (worst pain imaginable).

If the patient developed nausea or vomiting in the postoperative period, then metoclopramide 10 mg was given slowly intravenously as rescue antiemetic. If the patient's PONV persisted despite administering rescue antiemetic, the physician was allowed to give any other antiemetic as per their discretion. All the patients received paracetamol infusion 1 gm iv 4 times a day for the first 24 hours followed by paracetamol tablet 1 gm 4 times a day orally. If they complained of pain ≥5 on VAS, Ketorolac 30 mg i/v was used as a breakthrough analgesic the patients were enquired about the common side effects of medication, namely, headache, dizziness, drowsiness, constipation, and flushing.
The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0. Continuous variables were expressed as Mean ± SD and categorical variables were summarized as frequencies and percentages. Student's independent t-test was employed for comparing continuous variables. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. A P-value of less than 0.05 was considered statistically significant.

Results

60 patients were randomly allocated to group MP and group MG, as 30 patients in each. The patient's characteristics, duration of surgery or anaesthesia, incidence of motion sickness or history of PONV, and non-smoking status were comparable and difference was not significant between the two groups. The calculated simplified risk score of Apfel was also comparable between the groups.

Table 1: Patient characteristics, surgery and anaesthetic data

Characteristics	Group MP (n=30)	Group MG (n=30)	P Value
Age [years]	31.2+3.52	29.9+2.87	0.122
Weight [kgs]	58.3+4.62	57.8+2.61	0.608
Sex [M/F]	17/13	21/09	0.284
Non Smoker	22	19	0.405
H/O motion sickness or PONV	03	06	0.469
Duration of Anaesthesia [min]	203+14.73	198+10.91	0.141
Duration of Surgery [min]	192+9.87	189+7.42	0.189

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 palonosetron group compared to the methylprednisolone and granisetron group.
The incidence of vomiting and use of rescue antiemetic was not different between the groups. 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 palonosetron group had a complete response compared to the methylprednisolone and granisetron group [70% vs 43.3%]. Between 24 and 48 h, the incidence of nausea and vomiting was more or less same in both the groups (7% vs 14%). Overall, higher number of patients had a complete response in the methylprednisolone and palonosetron group compared to granisetron group (87% vs. 44%).

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

	First 2 Hours			First 2-24 Hours			First 24-48 Hours		
	Group MP	Group MG	P Value	GroupMP	Group MG	P Value	GroupMP	Group MG	P Value
Nausea: Mild/Moderate/Severe	1/3/2	1/2/1	0.729	3/3/2	5/7/6	0.009*	0/3/1	3/5/2	0.067
Vomiting	6	4	0.729	4	9	0.210	2	4	0.671
Rescue Antiemetic	5	2	0.421	5	8	0.347	3	7	0.298
No PONV	19	24	0.152	21	13	0.037*	26	13	0.001*

*Statistically significant Difference (P-value<0.05)

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Incidences of side effects were slightly less specific in palonosetron-methylprednisolone group than the granisetron-methylprednisolone group.

Table 3: Side effects

No Side Effects	GroupMP	Group MG	P Value
Headache	3	5	0.704
Dizziness	1	2	1.000

There was no significant difference in the pain scores between the groups.

Table 4: Pain scores

VAS score	GroupMP	Group MG	P Value
In first 2 hours	2.0+1.12	1.7+0.91	0.259
In 2-24 hours	2.7+0.94	3.0+0.87	0.205
In 24-48 hours	2.8+1.17	3.2+1.24	0.204

Discussion

PONV results in morbidity like wound dehiscence, bleeding from surgical site, pulmonary-aspiration of gastric contents, fluid imbalance and electrolyte disturbances, delayed recovery and hospital discharge and decreased patient satisfaction[12]. The recommended pharmacologic antiemetic for PONV prophylaxis in adults include the 5-HT3 receptor antagonists (ondansetron, dolasetron, granisetron, tropisetron, ramosetron, and palonosetron), neurokinin-1 (NK-1) receptor antagonists (aprepitant, casopitant, and rolapitant), corticosteroids (dexamethasone and methylprednisolone), butyrophenones (droperidol and haloperidol), antihistamines (dimenhydrinate and meclizine), and anticholinergics (transdermal scopolamine)[13].

Apfel devised a simple risk scoring system for predicting PONV using four major risk factors namely: female sex, prior history of motion sickness or PONV, non-smoker, use of postoperative opioids[14].

The cause of PONV after middle ear surgeries is multifactorial. There are abundant 5-HT3 receptors present in the vicinity of trigeminal nerve and vestibular labyrinth; hence, 5-HT3 receptor antagonists are efficacious in middle ear surgeries. The 5-HT3 antagonists have been proved to be an efficacious antiemetic in decreasing the incidence PONV after middle ear surgery [1]

It is advocated that the drugs with different mechanisms of action should be used in combination to optimize the efficacy. Preoperative glucocorticoid has been shown to decrease the PONV and postoperative fatigue associated with laparoscopic cholecystectomy [15]. A recent meta-analysis reported that perioperative steroids in knee arthroplasty significantly reduce postoperative pain. Both low (40 mg) and high (125 mg) doses of methylprednisolone have been shown to be effective in reducing PONV [16,17].

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]. Due to the stimulation of the labyrinth, PONV continues for longer duration in middle ear surgeries. Granisetron has been shown to be more effective in prevention of early but not late PONV due to the shorter duration of action of granisetron (4 h), whereas corticosteroids have shown to have more evident action in the prevention of late PONV[18].

Palonosetron is a relatively newer 5-HT3 receptor antagonist which is proposed to be more potent and a longer duration of antiemetic action than the granisetron. 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 palonosetron is also longer than that of granisetron (9 h vs. 3.5 h) [19].

We noted that the combination of two antiemetics, palonosetron and methylprednisolone, had better efficacy than granisetron and methylprednisolone when used as a prophylaxis against PONV especially in the first 24 hours. But the overall incidence of post-operative nausea vomiting was significantly decreased in the methylprednisolone -palonosetron group. Present study was one of its kind, as above combinations were never compared to prevent PONV in middle ear surgeries.

Limitations of our study were small sample size and done in only specific surgeries. The results of our study may be applicable to all the surgeries with expected long duration of nausea and vomiting after larger sample studies.

Conclusion

Combination of methylprednisolone and palonosetron is superior to methylprednisolone and granisetron

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for prevention of PONV after middle ear surgery. Therefore, we recommend combination of methylprednisolone and palonosetron for prophylaxis for PONV in middle ear surgeries.

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