A prospective, randomised, double blind controlled comparative study of antiemetic effects of ramosetron and dexamethasone with ondansetron and dexamethasone combination for prevention of post operative nausea and vomiting in patients undergoing middle ear surgery

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Abstract

Introduction: Post operative nausea and vomiting (PONV) is one of the most frequent complications of middle ear surgery that can result in adverse physical and psychological outcomes. Various antiemetic combinations are tried for prophylaxis in high risk patients. Commonly a combination of dexamethasone and 5HT3 antagonists are used as antiemetics for preventing nausea and vomiting. We studied the efficacy of various drug combinations using dexamethasone, ondansetron and ramosetron for prevention of PONV for 24 hours post operatively in patients undergoing middle ear surgery.

Aims and Objectives: To study the PONV incidence and to evaluate the efficacy of combination of ramosetron and dexamethasone in comparison to combination of ondansetron and dexamethasone and dexamethasone alone after general anaesthesia in patients undergoing middle ear surgery.

Materials and Method: Ninety adult patients of American Society of Anaesthesiologists(ASA) class I and II undergoing middle ear surgery were divided randomly into three equal groups of 30 patients each. Group DO (Dexamethasone 8 mg + Ondansetron 4 mg), Group DR (Dexamethasone 8 mg + Ramosetron 0.3 mg) and Group DS (Dexamethasone 8 mg and saline). The incidence of PONV and severity of PONV, the need for rescue antiemetic therapy were observed at 0-6, 6-12, 12-18 and 18 -24 hours postoperatively.

Results: The nausea and vomiting incidence was lower in Group DR in comparision to Group DO (3.33% vs 30% p= 0.044). It was much more lower in comparision to Group DS (3.33% vs 56% p = 0.000) which was highly significant in 0-6 hours postoperatively. Rescue antiemetic therapy requirement was nil in the Group DR, 16.7% in the Group DO and 50% in Group DS. In Group DR the complete response was higher in comparision to Group DO.

Conclusion: Ramosetron and dexamethasone combination is preferable to ondansetron and dexamethasone combination for prevention of nausea and vomiting in the post operative period after middle ear surgery.

Keywords: Middle ear surgery, PONV, Dexamethasone, Ondansetron, Ramosetron

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Introduction

PONV is a commonly experienced problem and one of the frequently encountered distressing symptoms in the post operative period. Incidence of PONV is 20 - 30% in patients undergoing surgery under general anaesthesia using inhalation agents. Postoperative nausea and vomiting (PONV) incidence is very high following middle ear surgeries due to stimulation of labyrinth.(1) 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.(2) Among 5HT3 antagonists, ondansetron is popular because of its efficacy and safety when compared with other antiemetics. It provides significant reduction in early PONV.(3)

Dexamethasone, when used with 5HT3 antagonist, reduces the absolute risk of PONV to minimum. For high risk group patients, 5HT3 receptor antagonists and dexamethasone combination has been recommended for prophylaxsis.(4) To reduce late PONV dexamethasone has been preferably used.(5,6,7) As a cost effective alternative to ondansetron, dexamethasone is also used prophylactically.(7) Dexamethasone and ondansetron combination therapy is the preferred choice for prevention of PONV after middle ear surgery.(8,9) In other surgeries for reducing early as well as late PONV, the newer 5-HT3 antagonist ramosetron, has been found to be more effective than ondansetron because of its long duration of action.(10) Though many studies have concluded that ramosetron has similar or better efficacy compared to ondansetron, but there are few studies comparing the combination therapy of dexamethasone with ondansetron or ramosetron for PONV prophylaxis for middle ear surgeries.

Therefore, we conducted this study to compare dexmethasone and ondansetron combination therapy to dexmethasone and ramosetron combination for prevention of PONV up to 24hrs after middle ear surgeries.

Materials and Method

Approval from institutional ethical committee was obtained. After taking a written and an informed

consent, ninety patients in the age group of 18 to 60 years of American Society of Anaesthesiologists (ASA) physical status I and II, posted for middle ear surgery in Krishnarajendra hospital were included in our study. Patients were randomly allocated by a computer – generated randomisation table into three groups - Group DO(n=30) received Dexamethasone 8 mg + Ondansetron 4mg, Group DR (n=30) received Dexamethasone 8 mg +Ramosetron 0.3 mg, Group DS (n =30) received Dexamethasone 8 mg + Saline.

All the patients received oral Diazepam 10 mg and Ranitidine hydrochloride 150 mg the night before surgery. In the operation theatre, the basal vital parameters (NIBP, SPO2, ECG) were recorded. All the subjects were premedicated with inj Midazolam 1 mg and inj Fentanyl (2 mcg/kg) intravenously. Study drug Dexamethasone 8 mg was administered just before induction of general anaesthesia. Induction was performed with propofol (2mg/kg) and vecuronium(0.1mg/kg). The patients were intubated and anaesthesia was maintained with 33% Oxygen, 66% nitrous oxide and isoflurane 1 – 1.5%. End tidal concentration of CO2 was maintained between 35 to 40 mm of Hg. The patient received intravenous paracetamol 1 gm infusion during the surgery. The patient's heart rate and blood pressure were monitored every 5 minutes during the surgery. Patients received ondansetron 4 mg (2 ml) or Ramosetron 0.3 mg (diluted to 2 ml) or Saline (2 ml) near the end of surgery. After surgery reversal was given with neostigmine (0.05 mg / kg) and glycopyrrolate (0.02 mg/kg). Trachea was extubated after clinically assessing the adequacy of neuromuscular blockade reversal. Intramuscular Inj. Diclofenac sodium 75mg was given for post operative analgesia.

The incidence of nausea and vomiting in the first 24 hours of post operative period was observed, this was the primary efficacy variable. The secondary efficacy variable was the use of rescue antiemetic therapy. These parameters were assessed by an observer who was blinded to the study. PONV assessment was performed depending on the severity every hourly in the first 6 hours, three hourly in 6-12 hours and sixth hourly in 12 – 24 hours postoperatively using the following PONV scoring system.[11] Score 0 – no nausea, Score 1 – nausea only, Score 2 – nausea with retching, Score 3 – vomiting. Nausea was defined as a subjectively unpleasant sensation associated with an urge to vomit, Retching was defined as spasmodic rhythmic contraction of the respiratory muscles without expulsion of gastric contents.[12] Vomiting was defined as the forceful expulsion of gastric contents.[12] Nausea and vomiting occurring within the first 6 hours was considered as early nausea and vomiting.[13] Vomiting and retching episodes separated by less than 5 minutes is taken as a single episode. Nausea and vomiting occurring within the first 6 hours was defined as early PONV and between 6 – 12 hours as delayed PONV. Complete response was defined as absence of nausea, retching, vomiting without using rescue antiemetic.[13] All patients who had nausea with retching or vomiting were given intravenous Metaclopromide10mg as the rescue antiemetic. Patients were also observed for adverse effects like drowsiness, sedation, headache, dizziness, flushing in the post operative period for 24 hours.

Data obtained from the study groups was statistically analysed using Anova, Cramer's V Test and independent sample T test with SPSS Version 20.0. P value less than 0.05 was considered significant. All values are expressed as mean ± standard deviation, number of patients or percentage.

Results

This prospective, randomised double blind study was conducted on 90 adult patients of ASA I and II posted for middle ear surgery under general anaesthesia. Demographic characteristics like age, sex, height, weight and body mass index were comparable between the groups. The duration of anaesthesia or duration of surgery were similar between the groups. Blood pressures were recorded throughout the surgery and mean of the readings were taken from every group. Haemodynamic parameters were comparable between the groups and the difference observed was statistically insignificant.

Table 1: Demographic data

	Group DS	Group DO	Group DR	P Value
Age in Years(SD)	28.80±7.02	28.86±9.60	27.13±8.32	0.664
Gender (F/M)	19/11	18/12	20/10	0.866
Weight in KGS(SD)	60.23±8.70	56.16±8.20	55.10±9.19	0.060
Height in CMS(SD)	163.63±8.43	158.90±8.83	158.36±8.15	0.034
BMI KG/M2(SD)	22.86±2.38	22.44±2.19	22.16±2.96	0.560
Duration of Anaesthesia	185.50±8.54	184.83±9.04	186.16±9.43	0.849
Duration of Surgery	169.50±9.85	166.40±9.19	166.40±9.19	0.343

Table 2: **Incidence of PONV in first 6 hours and comparision between the groups**

Score	Group DS n =30	Group DO n =30	Group DR n =30	DS vs DO	DS vs DR	DO vs DR
0	13	21	29	P- 0.224 Not significant	P- 0.000** Highly significant	P-0.044* Significant
1	7(23%)	4(13%)	1(3%)			
2	4	2	0			
3	6	3	0			

* Significant, ** Highly significant

Nausea and vomiting was significantly higher in the DS group and DO group when compared to the DR group in the first 6 hours. Complete response was noted in 43%, 70% and 97% of patients in the DS group, DO group and DR group respectively.

Table 3: Incidence of PONV in 6 – 12 Hours and comparision between the groups

Score	Group DS n =30	Group DO n =30	Group DR n =30	DS vs DO	DS vs DR	DO vs DR
0	19	29	30	P-0.014*	P-0.004**	P-0.313
1	7	1	0			
2	1	0	0			
3	3	0	0			

* significant, ** highly significant

No statistically significant difference was found between Group DO and Group DR for PONV in the next 6 hours. However, significant difference was noted in the DS group when compared to the DR group. Complete response was found in 63%, 97% and 100% in the DS, DO and the DR groups respectively.

Table 4: Incidence of PONV in 12-18 Hours and comparision between the groups

Score	Group DS n =30	Group DO n =30	Group DR n =30	DS vs DO	DS vs DR	DO vs DR
0	25	30	30	P-0.065	P-0.065	P-0.313
1	4	0	0			
2	1	0	0			
3	0	0	0			

Table 5: Incidence of PONV in 18-24 Hours and comparision between the groups

Score	Group DS n =30	Group DO n =30	Group DR n =30	DS vs DO	DS vs DR	DO vs DR
0	27	29	30	P- 0.301	P-0.076	P-0.313
1	3	1	0			
2	0	0	0			
3	0	0	0			

The incidence of PONV between 12 to 24 hours was lower in the DS, DO and DR groups. Complete response observed was 83%, 97% and 100% in the DS, DO and the DR Groups respectively. Though the incidence of nausea and vomiting was more in the DS group when compared to the DO and DR Group between 12 -24 hours, it was not statistically significant.

Table 6: Requirement of rescue antiemetic

Group	Percentage
DS	50%
DO	16.7%
DR	0

The rescue antiemetic (Inj Metaclopromide 10mg) therapy necessity was higher in the DS Group (50%) when compared to DO Group(16.7%) and was nil in the DR Group. The adverse effects were not observed in all the three groups at any time interval during the study period.

Discussion

PONV occurs frequently in gynaecological, obstetric, breast and middle ear surgeries.[14] PONV is a frequent complication after middle ear surgeries, with an incidence up to 80% when no antiemetics are used.[2] Dexamethasone was found to be an effective antiemetic in patients undergoing chemotherapy with limited side

effects.[15,16] The mechanism of action of corticosteroids is unknown but, may be related to inhibition of prostaglandin synthesis, decrease in the 5HT3 levels in the central nervous system or by an anti inflammatory action at operative sites.[17,18,19] Animal experiments suggest that it exerts its antiemetic effects through central inhibition of the nucleus tractus solitarii but not the area postrema.[20] PONV is multifactorial and combination drug therapy with different mechanisms of action is more effective.[21] For patients at increased risk of PONV, the combination therapy using 5HT3 receptor antagonist with another antiemetic drug having a different mechanism and site of action is recommended.

SAMBA guidelines[22] suggest that adults at moderate risk for PONV should receive combination therapy with one or more prophylactic drugs from different classes. It is also found that combinations act synergistically. Single drug therapy has frequent failure rates in situations with severe and frequent PONV.[14,22] Combination therapy is superior when compared to monotherapy for PONV prophylaxis.[14,22] In view of these observations, in the present study combination of antiemetics was employed.

For PONV treatment and prevention, Ondansetron was the first 5HT3 receptor antagonist to become clinically available. But when compared with other 5HT3 antagonists Ondansetron is less selective for the 5HT3 receptor. It binds to 5HT1B, 5HT1C alpha adrenergic and opioid receptors with low affinity.[10] It was revealed by a systematic review that Ondansetron's prophylactic effect on nausea was less pronounced when compared to vomiting.[10] The combination of Dexamethasone and Ondansetron was considered as the optimum choice for prevention of PONV after middle ear surgery.[8] This was because of the different mechanisms by which the drugs act in controlling PONV.

Ramosetron is a recently developed 5HT3 receptor antagonist with a higher affinity and longer duration of action compared with other 5HT3 receptor antagonists.[23] The elimination half life of Ramosetron (9.3h) is longer in comparison to Ondansetron (3.5h), Granisetron(4.9h) and Alosetron(3.0h).[23,24] Ramosetron has a higher affinity (Ki = 0.091) and slower dissociation rate for 5HT3 receptors compared with other 5HT3 receptor antagonists.[25] The active metabolite M1 maintains a high receptor occupancy and prolongs the duration of action.[23]

In present study, there was clinical and statistical significance in the incidence of PONV in between the groups in the first 6 hours. When compared to DS and DR group the incidence of PONV is decreased in the DR group, which is statistically highly significant (p= 0.000). When compared to the DO and the DR group the incidence of PONV is decreased in DR group which is also statistically significant (p= 0.044). When compared to the DS and DO groups, though the incidence of PONV was less in the DO group it was not statistically significant (p = 0.224).

There was statistical significance in the incidence of PONV in between the groups in 6 -12 hours. When compared to DS and DR group the incidence of PONV is decreased in the DR group, which is statistically significant(p= 0.004). When compared to the DO and the DR group the incidence of PONV is not statistically significant (p= 0.313). When compared to the DS and DO groups, the incidence of PONV was decreased in the DO group. It was significant statistically (p = 0.014).

Between 12 -24 hours the incidence of PONV was more in the DS group when compared to DO and DR group which did not reach statistical significance. When compared to the DO and the DR group the incidence of PONV is decreased in DR group which is statistically significant (p= 0.044). When compared to the DS and DO groups, though the incidence of PONV was decreased in theDO group it was not statistically significant (p = 0.224).

Our study is comparable with Sameer N Desai et al[26] study. They have observed that the incidence of PONV is higher in the DO Group when compared to DR Group in the first 24 hours, but it was not statistically significant. In our study, we observed the incidence of PONV is higher in the DO Group when compared to the DR Group in 24 hours, but it was statistically significant in the first 6 hours (p= 0.044). The lower incidence of nausea(3%) and no vomiting in the DR Group in first 6 hours may be explained by its potency and the administration of prophylactic Dexamethasone 8 mg prior to surgery. The onset time of Dexamethasone's antiemetic effect may be two hours and more than 50% of the patient's experience PONV in the first two hours post operatively.[29]

Our study is also comparable with Younghoon Jeon et al[27] study. They found that PONV rate was significantly lower in the combination group i.e., Ramosetron 0.3mg + Dexamethasone 8 mg than in the Dexamethasone alone Group (p=0.006). In the current study we observed that PONV rate was significantly lower in the DR Group when compared to the DS Group (p= 0.000) in the first 6 hours. We also noted that incidence of PONV was lower in DO Group (30%) when compared to the DS (57%) Group. Our results were also comparable to S. I. Kim et al[28] study who found that the incidence of nausea was less in the Ramosetron (50%) and Ondansetron Group (44%) Groups in comparison to the placebo group(69%) (p< 0.05). In addition, the incidence of vomiting was lower in both the Ramosetron (17%) and the Ondansetron (20%) Groups than in the placebo Group (44%) in 24 hours after surgery (p < 0.05). Only saline was used as placebo in their study whereas we used saline + Dexamethasone in our control group.

Dinesh Govinda Rao et[29] al in their study found complete response in 90% in OD Group and 100%in

RD Group in 6-12 hour period and in the 12- 24 hour period complete response was 97% in OD Group and 100% in RD Group. These results were comparable with our study. We found complete response in 97% in DO and 100% in DR group in 6 - 12 hours and 97% and 100% in DO and DR Groups respectively in 12 – 24 hours.

Our study is also comparable to Lee et al[10] study in thyroid surgeries under general anaesthesia, they used Ramosetron and Dexamethasone for PONV with ramosetron alone. They concluded that combination therapy is better than single drug therapy for PONV.

The requirement of rescue antiemetics was higher in the DS Group (50%) when compared to DO Group(16.7%) and was nil in the DR Group. The adverse effects like headache, dizziness, drowsiness, flushing or sedation were not observed in all the three groups at any time interval during the study period.

Conclusion

Combination of Dexamethasone 8 mg with antiemetic 5HT3 receptor antagonists Ramosetron (0.3mg) or Ondansetron (4mg) decreases the incidence of PONV and the requirement for rescue antiemetic therapy in the first 24 hours post operatively. However, Dexamethasone and Ramosetron combination has better efficacy than Dexamethasone and Ondansetron combination in decreasing PONV after middle ear surgery

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