

Comparative study of granisetron and ondansetron alone and their combination with dexamethasone, for prevention of PONV in middle ear surgery

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Abstract

Introduction : Our study focuses on post-operative nausea and vomiting (PONV) in middle ear surgery, a horrible experience to both doctors and patients. We compared the efficacy of granisetron and ondansetron alone and their combination with dexamethasone, for prevention of PONV in middle ear surgery.

Methods: 125 patients (63 females, 62 males) with a age group between 10 to 60 years , who underwent middle ear surgery were randomly allocated and divided into 5 groups (25 patients in each group) according to the drug they receive i.e, Group-A (control group-no antiemetic), Group-B (granisetron 40mcg/kg), Group-C (granisetron 40mcg/kg + dexamethasone 8mg), Group-D (ondansetron .1mg/kg), Group-E (ondansetron .1mg/kg+ dexamethasone 8mg). After a standard protocol used in all of them, all the groups were evaluated for post-operative nausea , retching and vomiting and their side effects immediately at extubation for 24 hours of anesthesia.

Results: The incidence of PONV is different in all groups i.e., maximum in group A (76%) followed by group D (28%), then group B (16%), then group E (12%) and minimum in group C (8%) and statistically significant ($p < .001$). The incidence of PONV was maximum during first 6 hours, but group B & group C showed higher incidence during first 12 hours whereas group D showed higher incidence during late post- operative period.

Conclusion: Prophylactic combination antiemetic therapy of granisetron (40mcg/kg) dexamethasone (8mg) was found to be superior to individual therapy of granisetron and ondansetron and combination therapy of ondansetron (.1mg/kg) and dexamethasone (8mg) in middle ear surgery

INTRODUCTION

Postoperative nausea and vomiting (PONV) are one of the most common complications after anesthesia and surgery, especially after middle ear surgery, laparoscopic cholecystectomy, emergency laparotomy etc. PONV increases postoperative morbidity to the patients like tension on the sutures, bleeding at operation site, aspiration pneumonia, fluid electrolyte imbalance, dehydration and increases the hospital stay as well.

Newer antiemetic agents like Ondansetron and Granisetron, selective competitive antagonist of 5- hydroxytryptamine-3 receptor, were used successfully to treat post operative nausea and vomiting ^{1,2,3,4,5,6,7} . Dexamethasone, a

glucocorticoid, can be used as adjunct to antiemetics. It causes better control of late PONV ⁹, by inhibition of prostaglandin synthesis ⁸, decrease in 5 HT levels in CNS ¹⁰ or by anti-inflammatory actions at operative sites ¹¹. Fuji et al in 1999 proved the better efficacy of Granisetron + Dexamethasone than Granisetron alone for prevention of nausea and vomiting in pediatric surgery.

Despite different background factors (age, sex ,h/o motion sickness, h/o PONV in previous surgery, menstrual cycle etc.) and intraoperative factors (i.e. premedication, inducing agent, duration of surgery, pain management) high incidence of emesis is associated in middle ear surgery and is likely to be caused by activation of vestibular afferent

pathway involved in motion sickness.

To our knowledge combination therapy of antiemetic agents were not studied adequately in middle ear surgery. So this investigation was designed to compare the efficacy combination therapy of antiemetic with dexamethasone with antiemetic alone in middle ear surgery.

MATERIAL & METHODS

After approval of institutional review board and ethics committee, 125 patients ASA grade I & II scheduled for elective middle ear surgery, were prospectively included in the study. Exclusion criteria comprised gastrointestinal disorders, pregnancy or menstruation, h/o motion sickness or previous h/o PONV and age below 10 or more than 60 years.

Patients were randomly allocated into five groups (5 patients each) according to the drug they received for prevention of PONV. The groups are,

- 1) Group A: Control group (no antiemetic)
- 2) Group B: Patient receiving granisetron 40 mcg/kg diluted in 5ml of NS
- 3) Group C: Patient receiving granisetron 40mcg/kg plus dexamethasone 8mg diluted in 5ml of NS.
- 4) Group D: Patients receiving ondansetron 0.1mg/kg diluted in 5ml of NS.
- 5) Group E: Patients received ondansetron 0.1mg/kg plus dexamethasone 8mg diluted in 5ml of NS.

All patients were premedicated with oral alprazolam (0.25 mg) and ranitidine (150mg) in the night before surgery. Patients were induced with fentanyl (2mcg/kg), thiopentone sodium (5mg/kg) and vecuronium bromide (0.1mg/kg). After endotracheal intubation anesthesia was maintained with O2:N2O=30:70 and halothane (.5%-1%). Intermittent boluses of fentanyl (1mcg/kg) at an interval of 30 minutes were used for analgesia intraoperatively.

Residual neuromuscular blockade of vecuronium was antagonized with neostigmine (.05mg /kg) Glycopyrolate (10mcg/kg) at the end of surgery. Extubation done when the patient is awake and respiration is adequate and regular. Diclofenac Sodium was used for postoperative pain relief.

Any episode of post-operative nausea, vomiting or retching experienced by the patient were recorded within 24 hours of

anesthesia i.e. immediately at extubation and thereafter at post op ward at following time intervals : 0-2 hours, 2-6 hours, 6-12 hours and 12-24 hours. Other details of adverse effects of drug like headache, giddiness, extra pyramidal symptoms, allergic reaction, urinary retention etc. were also followed up.

To assess severity of PONV the scoring system was evolved which was as following ----

- No nausea ----- Score 0
- Nausea only ----Score 1
- Nausea with retching ----- Score 2
- Vomiting -----Score 3

STATISTICAL ANALYSIS

The incidence of PONV / retching was found different in each groups. In each group, the incidence of PONV was compared between male and female population and total PONV scoring was done. The inter-group comparison for PONV was done by using chi-square test where group A was found higher PONV than all other groups (p<.001).

RESULTS

Figure 1

Table 1: Demographic data

	Group A	Group B	Group C	Group D	Group E
Number of patients	25	25	25	25	25
Mean age(years)	21.24±9.09	26.28±12.24	26.60±9.84	29.76±11.53	27.54±10.91
Mean weight(kg)	39.94±13.16	50.86±14.46	48.89±12.67	53.68±12.37	51.63±15.01
Male	10	9	19	13	11
female	15	16	6	12	14
Mean duration of anesthesia(min.)	131.25±26.60	120.00±26.54	122.10±37.01	135.00±37.50	132.50±24.49

The difference of demographic data in relation all five groups regarding mean age, body weight, sex distribution and mean duration of anesthesia was not statistically significant in our study.

Figure 2

Table 2: Comparison of incidence of PONV among different groups

Groups	Total no of patients	Patients with nausea and vomiting	Patients without nausea and vomiting
A	25	19(76%)	6(24%)
B	25	4(16%)	21(84%)
C	25	2(8%)	23(92%)
D	25	7(28%)	18(72%)
E	25	3(12%)	22(88%)

Figure 3

Table 3: Comparison of incidence of PONV among different groups according to sex distribution

Groups	Total no of patients	sex	No of patients	No of patients with nausea and vomiting	% of patients without nausea and vomiting
A	25	male	10	4	40
		female	15	14	96
B	25	male	9	2	22.5
		female	16	2	12.5
C	25	male	19	0	0
		female	6	2	33
D	25	male	13	3	22
		female	12	4	33
E	25	male	11	1	9
		female	14	2	14.2

The incidence of PONV differ significantly in groups, the maximum in group A (76%), then group D (28%), followed by group B (16%), group E (12%) and minimum in group C (8%). Incidence of nausea and vomiting in male is maximum in group A (40%), followed by group B and Group D (22%), (9%) in group E and nil in group C. But in females this maximum in group A (96%), followed by group C & D (33%) then group E (14.2%) and minimum in group B (12.5%) (P<.05).

Figure 4

Table 4: Incident of emetic episodes among different groups at different visits

Post-operative visits	Group-A	Group-B	Group-C	Group-D	Group-E
At extubation	5	0	0	0	0
0-2hours	13	0	3	1	0
2-6 hours	11	6	0	2	7
6-12 hours	8	1	3	4	0
12-24 hours	6	0	0	5	2

The incidence of PONV was maximum at during first 6 hours post-op, highest in group A. In group B & C the incidence of emetic episodes are higher during first 12 hours post-op. than later half. In group D emetic episodes are higher in late post-op whereas in group E the incidence of emesis is little higher during 2-6 hours of post-operative period with better control of early nausea and vomiting.

DISCUSSION

Post-operative nausea and vomiting are one of the most common complications after anesthesia and surgery with a relative high incidence (60-80%) after middle ear surgery . These high incidences justify the use of prophylactic antiemetic for prevention of PONV after middle ear surgery.

In our study group A (placebo) incidence of PONV was 76% same as reported by Reinhart & Honkawaara in 1994^{6,12} in their study (62-80% in placebo group). The incidence of PONV in group B was significantly decreased (16%) after receiving Granisetron as prophylactic antiemetic before induction. Fuji et al 1998¹³, conducted a similar study using Granisetron where complete response was found in 85% of cases.

In another study by Fuji et al in 1998¹⁴ to compare the effectiveness of granisetron plus dexamethasone and dexamethasone alone for prevention of PONV in middle ear surgery, complete response was found in 98% patients with Granisetron plus dexamethasone (P<.05). In group C complete response was observed in 92% of cases in our study. PONV, noted in only adult female (8%) in this group, could be due to fluctuation in female sex hormone. The precise mechanism of augmentation by dexamethasone remains unclear, but Granisetron antagonizing 5-HT3 receptor is associated with antiemetic activity¹¹ and dexamethasone may also inhibit stimulation of 5-HT3 receptor^{8,16}

In group D & E complete response was observed in 72% and 88% cases respectively. Regarding the timing of administration of Ondansetron, there are reports, which prove its effectiveness is more when given prior to induction of anaesthesia¹. The combination of ondansetron plus dexamethasone reduces incidence of emetic episodes better than ondansetron alone. It causes better control of delayed nausea and vomiting and rather than early PONV.

Our Study showed that nausea and vomiting in Group D is higher (28%) than group B (16%). Delayed nausea and vomiting are better controlled in group B than group D probably because of longer duration of action of granisetron than ondansetron. Episodes and scoring of nausea, vomiting and retching are high in group D and group B (Score 17 & 13 respectively).

The incidence of PONV in females is significantly high ($p < .001$) than male (see table-3). This difference has been attributed to fluctuation in female sex hormone concentration during menstrual cycle^{17,18}.

None of the antiemetic in our study led to any significant hemodynamic changes or any adverse effect. The most common complaint by the patients was headache (10%), not varying significantly among different groups. Sendery et al (1993)¹⁹ and McKenzie et al (1993)²⁰ found the incidence of headache ranging from 16-21%, comparable to our study results in group A (16%) and group B (12%). The known side effect of 5-HT₃ antagonist include headache, light headedness, warm sensation in flushing and constipation.

Post-operative shivering was complained by 2 patients in group A and 1 patient in group D. No shivering was found in both Dexamethasone treated group.

CONCLUSION

In our study, it was observed that group C (granisetron + dexamethasone) is the best for prevention of PONV in middle ear surgery, followed by group E (ondansetron + dexamethasone) followed by group B (granisetron) and then group D (ondansetron). Dexamethasone may be used as a component of combined prophylaxis for control of PONV in patients undergoing middle ear surgery because of potentiating effect of antiemetic agent, partial analgesic effect and anti-inflammatory action in surgical site.

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References

1. Kovac A, McKenzie R, O'Connor T, Duncalf D, Angle J, Gratz T et al Prophylactic intravenous ondansetron in female outpatients undergoing gynaecological surgery : a multicentre dose-comparison study. *European Journal of Anaesthesiology* 1992; 9 (Suppl. 6): 37-47.
2. Dershwitz M, Roscow CE, DiBiae PM et al. Ondansetron is effective in decreasing postoperative nausea and vomiting. *Clin Pharmacol Ther.* 1992; 82: 96-101.
3. Haigh CG, Kaplan LA, Durham JM et al. Nausea and vomiting after gynaecological surgery : a meta-analysis of factors affecting their incidence. *Br J Anaesth* 1993; 71: 517-22.
4. Raphael JH and Norton AC. Antiemetic efficacy of prophylactic ondansetron in laparoscopic surgery: randomized, double blind comparison with metoclopramide. *Br J Anaesth* 1993; 71: 845-848.
5. Rust M and Cohen LA. Single oral dose ondansetron in the prevention of postoperative nausea and emesis. *Anaesthesia* 1995; 69 (Suppl.) : 16-23.
6. Honkavaara P, Saarinavaara L, Klemola U-K. Prevention of nausea and vomiting with transdermal hyoscine in adults after middle ear surgery during general anaesthesia. *Br J Anaesth.* 1994; 73: 763-66.
7. Paech MJ, Pavy TJ, Evans SF. Single dose prophylaxis for postoperative nausea and vomiting after major abdominal surgery, ondansetron versus droperidol. *Anaesth Intensive Care* 1995 Oct; 23 (5): 548-54.
8. Apro BMJ, Plezia PM, Alberts DS, Graham V, Jones SE, Suwit EA, Moun TE. Double blind crossover study of the antiemetic, efficacy of high-dose dexamethasone versus high-dose metoclopramide. *Journal of Clin Oncol.* 1984; 2: 305-520.
9. Schimmer BP, Parker KL. Adrenocorticotrophic hormone adrenocortical steroids and their synthetic analogs: inhibitors of the synthesis and actions of adrenocortical hormones. In : Goodman Gilman (Eds.). *The Pharmacological Basis of Therapeutics.* 9th ed. McGraw Hill 1996: 1459-85.
10. Young SN. Mechanism of decline in rate brain 5-hydroxytryptamine after induction of liver tryptophan pyrrolase by hydrocortisone: roles of tryptophan catabolism and kynurenine synthesis. *Br J. Pharmacol.* 1981; 74: 695-700.
11. McKenzie R, Tantisira B, Karambelkar DJ, Riley TJ, Abdelhady H. Comparison of ondansetron with ondansetron plus dexamethasone in the prevention of postoperative nausea and vomiting. *Anesth. Analg.* 1994; 79: 961-4.
12. Reinhart DJ, Klein KW, Schroff E. Transdermal scopolamine for the reduction of postoperative nausea in outpatient ear surgery: a double-blind, randomized study. *Anesth Analg.* 1994; 79: 281-284.
13. Fuji Y, Toyooka H, Tanaka H. Granisetron in the prevention of nausea and vomiting following middle ear surgery: a dose ranging study. *Br J Anaesth.* 1998; 81.
14. Fujii Y, Toyook H, Tanaka H. Prophylactic antiemetic therapy with combination of granisetron and dexamethasone in patients undergoing middle ear surgery. *Br J Anaesth.* 1998; 81: 754-756.
15. Carmichael J, Cantwell BM, Edwards CM, Zussmann BD, Thompson S, Rapeport WG, Harris AL. A pharmacokinetic study of granisetron (BRL 43694A), a selective 5-HT₃ receptor antagonist: correlation with antiemetic response. *Cancer Chemother. and Pharmacol.*

1989; 24: 45-59.

16. Aapro MS, Alberts DS. Dexamethasone as an antiemetic in patients treated with cisplatin. *New Eng J Med* 1981; 305: 520.

17. Bellville JW, Bross IJD and Howland WS. A method for the clinical evaluation of antiemetic agents. *Anaesthesiology* 1959; 73: 250-4.

18. Smessaert A, Schehr ES, Rustin GJS, Begent RHJ, Howells N, McQuade B, Bagshawe KD. Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin containing

chemotherapy. *Lancet* 1991; 338: 487-490.

19. Scuderi P, Wetchler B, Sung Y-F, et al. Treatment of postoperative nausea and vomiting after outpatient surgery with the 5-HT₃ antagonist ondansetron. *Anesthesiology* 1993; 78: 15-20.

20. McKenzie R, Kovac A, O'Connor T, Angel J, Gratz I et al. Comparison of ondansetron versus placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery. *Anesthesiology* 1993; 78: 21-28.

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