Randomized Double Blind Comparative Study Comparing Efficacy of Granisetron and Ondansetron for the Prophylactic Control of Postoperative Nausea and Vomiting in Patients Undergoing Middle Ear Surgery

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Abstract The objective is to evaluate the prophylactic profile, efficacy of granisetron and ondansetron to prevent postoperative nausea and vomiting (PONV) after middle ear surgery. In a randomized, double blind trial, one hundred patients undergoing middle ear surgery received either granisetron 1 mg or ondansetron 8 mg in equal volume ($n = 50$ for each) intravenously towards the end of surgery and before reversal of anaesthesia. A standard general anaesthetic technique was employed. Postoperatively, during the first 24 h after anaesthesia, the incidence of PONV, recovery score, time to first feeding, willingness to have the same prophylactic antiemetic drug in future and adverse events were recorded. The incidence of vomiting once (PONV score 2) was significantly less, 4% with granisetron and 22% with ondansetron ($P = 0.002$) respectively and the incidence of vomiting twice or more times in 30 min interval (PONV score 3) was significantly less, 8% with granisetron as compared to 34% with ondansetron ($P = 0.001$). The requirement of rescue antiemetic drug was significantly higher in ondansetron group, i.e. 34 vs. 8% in granisetron group ($P = 0.001$). The incidence of adverse events, recovery score and time to first feeding were comparable among the groups. Willingness to have the same prophylactic antiemetic drug in future was significantly high in patients receiving granisetron. Granisetron is more efficacious and desirable drug than ondansetron for reducing the incidence of PONV in patients undergoing middle ear surgery.

Keywords PONV · Ondansetron · Granisetron · Middle ear surgery

Introduction

Postoperative nausea and vomiting (PONV) occur frequently after middle ear surgery, with an incidence as high as 80% when no prophylactic antiemetic is given [1, 2]. This can cause significant patient discomfort, electrolyte disturbances, and may lead to delay in resumption of normal activities after elective surgery. The deleterious effects of PONV are not only limited to the patient's health but can also produce a negative financial impact on hospital resources and the patient. Of the available selective 5-HT₃ receptor antagonists, both granisetron and ondansetron reduce the incidence of PONV in patients undergoing general anaesthesia for middle ear surgery [3]. In this study, we have compared the efficacy of granisetron with ondansetron for the prevention of PONV and willingness to have the same prophylactic antiemetic drug in future in patients undergoing middle ear surgery.

Methods

After obtaining approval from the institutional ethics committee and written informed consent, we conducted a randomized double blind study in 100 ASA I or II patients (52 females) aged 18–65 years, undergoing middle ear surgery (tympanoplasty and mastoidectomy) under general anaesthesia.

All patients were divided into two groups—group 1 received ondansetron, group 2 received granisetron.

Patients with history of smoking, gastritis, heartburn, motion sickness, previous PONV, lower esophageal

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sphincter disorders, Ellison-Zollinger syndrome, uncontrolled hypertension, poorly controlled diabetes and preoperative emesis less than 6 h prior to surgery were excluded from the study.

Patients were randomly allocated to receive one of two-treatment regime respectively as: ondansetron 8 mg and granisetron 1 mg both given in same volume, i.e. 10 ml. These drugs were administered intravenously intravenously towards the end of surgery and before reversal of anaesthesia. A randomization list was prepared by a random number function in a computer spreadsheet and identical syringes containing each drug were prepared by personnel not involved in this study.

Patients received no preanaesthetic medication. Anaesthesia was induced with midazolam 1 mg, thiopentone sodium 5 mg kg⁻¹ and fentanyl 2 µg kg⁻¹ IV. Vecuronium bromide 0.2 mg kg⁻¹ was used to facilitate tracheal intubation. Anaesthesia was maintained with 1–3% sevoflurane (inspired concentration) and 66% nitrous oxide (which was replaced by air before closing the tympanic membrane) in oxygen. Ventilation was controlled mechanically and adjusted to maintain end tidal carbon dioxide concentration at 35–45 mmHg throughout surgery using an anaesthetic respiratory gas analyzer (Penlon AV800 ventilating machine, UK). Muscle relaxation was achieved with vecuronium as required. Temperature was monitored and maintained at 37 ± 1°C throughout surgery. The study drug was given 30 min before the reversal of anaesthesia. At the cessation of surgical procedure sevoflurane and nitrous oxide administration was stopped.

Residual neuromuscular blockade was antagonized with neostigmine 50–70 µg kg⁻¹ and glycopyrrolate 8–10 µg kg⁻¹ body weight and the trachea was extubated when the patient became awake. All patients received intramuscular injection of diclofenac sodium 75 mg stat and 8 hourly for postoperative pain relief. Postoperatively, all episodes of PONV were recorded within the first 24 h after anaesthesia at regular intervals (0–1, 1–2, 2–3, 3–4, 4–5, 5–6 and 6–24 h) by direct questioning by the attending anaesthesiologist without knowledge of which antiemetic the patient had received or by spontaneous complaint by the patients.

The time to first feeding and any other side effects were also noted in the postoperative period.

All patients were evaluated by using a PONV numeric scoring system

- 0 = No nausea/vomiting
- 1 = Nausea alone
- 2 = Vomiting once
- 3 = Vomiting twice or more times in 30 min interval.

Rescue antiemetic, ondansetron 8 mg intravenously, was given to all patients with PONV score of 3. Patient's

willingness to have the same antiemetic drug for the prevention of PONV in the future, was assessed at 24 h after surgery.

Statistical analysis was done using SPSS statistics package version 14. Parametric data was analyzed using the done by Student's *t*-test and categorical data was analyzed using the χ^2 test with Yate's correction factor. The computed '*P*' value less than 0.05 was considered as statistically significant.

Results

There were no significant differences between the groups with regard to age, sex, weight, height, sex, ASA physical status, duration of anaesthesia and surgery, type of surgery (tympanoplasty, mastoidectomy), preoperative PONV, intraoperative analgesic requirements, and time to first feeding. Large number of patients in both groups expressed a willingness to have the same antiemetic prophylaxis in the future but it was statistically significantly higher in granisetron group (*P* = 0.002) (Table 1).

During the first 24 h nausea only (PONV score 1) was present in 6 (12%) patients in the ondansetron group and 2 patients (4%) in granisetron group (*P* > 0.05). The patients who vomited once only (PONV score 2) was significantly higher, i.e. 11 (22%) patients in ondansetron group as compared to only 2 patients (4%) in granisetron group (*P* = 0.002). The patients who vomited twice or more times in 30 min interval (PONV score 3) during the first 24 h was significantly higher, i.e. 17 (34%) patients in the ondansetron group as compared to 4 (8%) patients in granisetron group (*P* = 0.001) (Figs. 1, 2, 3).

Rescue antiemetic was significantly higher, i.e. 17 (34%) patients in the ondansetron group as compared to 4 (8%) patients in the granisetron group (*P* = 0.001). No patient required repeat dose of rescue antiemetic drug.

No difference in adverse effects was noted in both the groups (Table 2).

Discussion

PONV are among the most common complications after anaesthesia and surgery, with a relatively high incidence after middle ear surgery (tympanoplasty or mastoidectomy [4, 5]. Honkavaara et al. [1] and Reinhart et al. [2] observed the incidence of PONV was as high as 60–80% in patients undergoing general anaesthesia for middle ear surgery. This incidence may justify the use of prophylactic antiemetics for the prevention of PONV after middle ear surgery [6, 7].

Table 1 Demographic profile

Parameter	Group 1	Group 2	P value
Age (years)	34.26 ± 13.77	32.48 ± 14.56	0.532
Weight (kg)	60.22 ± 6.876	60.66 ± 7.847	0.766
Height (cm)	164.44 ± 10.44	166.7 ± 10.250	0.276
Sex (M/F)	26/24	31/19	0.313
ASA physical status I/II	36/14	39/11	0.488
Types of operation performed			0.109
Tympanoplasty	29	21	
Mastoidectomy	24	26	0.689
Preoperative PONV	1/50	2/50	1.000
Total intraoperative dose of analgesics (fentanyl in µg)	121.3 ± 43.3	109.8 ± 37.14	0.509
Duration of anaesthesia (min)	179.44 ± 61.9	179.5 ± 62.45	0.981
Duration of surgery (min)	151.2 ± 61.4	152.7 ± 66.09	0.907
Time to first feeding (min)	216.07 ± 65.16	205.10 ± 55.74	0.368
Willingness to take same antiemetic drug	30/50	44/50	0.002

Data are expressed as mean ± standard deviation (SD), number and median

$P < 0.05$ significant

Fig. 1 Incidence of PONV score 1 **Fig. 2** Incidence of PONV score 2

The aetiology of PONV after middle ear surgery performed under general anaesthesia is not known, but is probably multifactorial. Several factors, including age, sex,

Fig. 3 Incidence of PONV score 3**Table 2** Incidence of adverse effects

Parameter	Group 1	Group 2	P value
Headache	1 (2%)	2 (4%)	0.558
Dizziness	1 (2%)	0	0.315
Drowsiness	0	0	*
Anxiety	1 (2%)	2 (4%)	0.558
Insomnia	2 (4%)	0	0.156
Total number of adverse effects	5 (10%)	4 (8%)	0.727

* Statistics not computed

Data are expressed as number (percentage)

$P < 0.05$ significant

obesity, history of motion sickness and/or previous PONV, menstruation, surgical procedures, anaesthetic technique and postoperative pain are considered to affect the incidence of PONV [8].

One of the causes of PONV after middle ear surgery could be the physical stimulus caused by the otologist

drilling and irrigating the bone adjacent to the inner ear. High levels of noise caused by drilling and suctioning have been reported in ear surgery, and noise exceeding 107 dB (A) has been measured in the mastoid cavity. The otologist also causes low frequency vibrations, especially when using a slowly rotating cutting burr. These vibrations may act in the same way as infrasound on the vestibular system. It has been shown that low-frequency sound stimulation provokes postural instability in patients undergoing surgery for chronic otitis media [9].

Irrigation with colder saline sets up thermal currents in the labyrinthine in one direction. While heat of burning can set up thermal currents in opposite direction. These thermal currents in labyrinthine fluids are irritants to the labyrinthine may cause vertigo and emesis.

In this study, however, these factors were well balanced between groups. Since increased middle ear pressure by nitrous oxide is also one of the surgical factors contributing to PONV, the middle ear pressure was optimized because nitrous oxide was replaced by air before closing the tympanic membrane. Therefore, the difference in complete response for emesis between the groups may be attributed to differences in the antiemetic drugs administered.

The incidence of PONV was 34% in ondansetron group and 8% in granisetron. Therefore, the difference in the incidence of the PONV among the groups can be attributed to the difference in the agents administered.

Our study coincides with the findings of various studies of Fujii et al. [6, 7, 10–12] where complete response rate were between 78 and 86% with varying doses of granisetron having the PONV 14–22%. PONV was much less in our study although we had used granisetron in lesser dose as compared to these studies.

Granisetron and ondansetron has been proved to be effective in the prevention of emesis induced by cancer chemotherapy [13] while Fujii et al. [14] had demonstrated that it also has potent antiemetic effect on PONV after middle ear surgery. Wilson et al. [15] had compared different doses of intravenous granisetron in the prevention of PONV and found optimal dose was 1 mg. In our previous study [16] we used this dose and found it effective. So, the same dose has been used in this study.

The major deficiency in this clinical trial was the failure to include a control group-receiving placebo. It has already been demonstrated that efficacy of granisetron is superior to placebo for preventing PONV after middle ear surgery. Furthermore, it has been reported that there is a poor quality of clinical information in placebo-controlled trials of ondansetron, one of 5HT₃ receptor antagonists, in the prevention of PONV. So, in this study, the control group-receiving placebo was not included.

The adverse effects observed in this study were relatively mild, and there was no difference in the incidence of

headache, dizziness, anxiety and insomnia. These were comparable to other studies.

In conclusion, granisetron is more effective, potent antiemetic and desirable drug for reducing PONV and good quality of recovery in patients undergoing middle ear surgery.

Conflict of interest None.

References

1. Honkavaara P, Saarivaara L, Klemola U-K (1994) Prevention of nausea and vomiting with transdermal hyoscine in adults after middle ear surgery during general anaesthesia. *Br J Anaesth* 73:763–766
2. Reinhart DJ, Klein KW, Schroff E (1994) Transdermal scopolamine for the reduction of postoperative nausea in outpatient ear surgery: a double blind, randomized study. *Anesth Analg* 79:281–284
3. Kovac AL (2006) Meta-analysis of the use of rescue antiemetics following PONV prophylactic failure with 5-HT₃ antagonist/dexamethasone versus Single agent therapies. *Ann Pharmacol* 40:873–887
4. Watcha MF, White PF (1992) Post operative nausea and vomiting, its etiology, treatment and prevention. *Anesthesiology* 77:162–184
5. Andrews PLR, Bhandari P, Davey PT, Bingham S, Marr HE, Blower PR (1992) Are all 5-HT₃ receptor antagonists the same? *Eur J Cancer* 28:S2–S6
6. Fujii Y, Toyooka H, Tanaka H (1997) Granisetron reduces the incidence of nausea and vomiting following middle ear surgery. *Br J Anaesth* 79:539–540
7. Fujii Y, Toyooka H, Tanaka H (1998) Granisetron in the prevention of nausea and vomiting following middle ear surgery: a dose ranging study. *Br J Anaesth* 80:764–766
8. Watcha MF, White PF (1992) Postoperative nausea and vomiting. Its etiology, treatment and prevention. *Anesthesiology* 77: 162–184
9. Ishizaki H, Pyykkö I, Aalto H, Starck J (1991) Tullio phenomenon and postural stability: EXPERIMENTAL study in normal subjects and patients with vertigo. *Ann Otol Rhinol Laryngol* 100:976–983
10. Fujii Y, Toyooka H, Kobayashi N (1999) Prevention of nausea and vomiting after middle ear surgery: granisetron versus ramisetron. *Laryngoscope* 109:1988–1990
11. Fujii Y, Toyooka H, Kobayashi N (2001) Prevention of postoperative nausea and vomiting with antiemetics in patients undergoing middle ear surgery: comparison of a small dose of propofol with droperidol or metoclopramide. *Arch Otolaryngol Head Neck Surg* 127:25–28
12. Fujii Y, Toyooka H, Tanaka H (1998) Prophylactic antiemetic therapy with granisetron, droperidol and metoclopramide in female patients undergoing middle ear surgery. *Anaesthesia* 53:1165–1168
13. Giglio CA, Soares H, Castro CP et al (2000) Granisetron is equivalent to ondansetron for prophylaxis of chemotherapy-induced nausea and vomiting. Results of a meta analysis of randomized controlled trials. *Cancer* 89:2301–2308
14. Fujii Y, Tanaka H, Toyooka H (1997) Granisetron reduces incidence of nausea and vomiting after breast surgery. *Acta Anaesthesiol* 41:746–749

15. Wilson AJ, Diemunsch P, Lindeque BG, Scheinin H, Helbo-Henson HS, Kroeks MVAM, Kong KL (1996) Single dose i.v. granisetron in the prevention of postoperative nausea and vomiting. *Br J Anaesth* 76:515–518
16. Dua N, Bhatnagar S, Mishra S, Singhal AK (2004) Granisetron and ondansetron for prevention of nausea and vomiting in patients undergoing modified radical mastectomy. *Anaesth Intensive Care* 32:761–764