

The Comparison of Effects of Intravenous Ondasetron and Granisetron on Postoperative Nausea and Vomiting in Middle Ear Surgery

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Abstract

Background: Middle ear surgery is prone for Postoperative nausea and vomiting (PONV), PONV is common and distressing adverse events associated with surgery and anesthesia. In patients undergoing Middle ear Surgery without antiemetic prophylaxis, the incidence of PONV is high and It has impact on postoperative recovery.

Objective: The aim of this study was to compare the effect of prophylactic antiemetic effects of ondansetron and granisetron in patients undergoing Middle ear surgery when these drugs are administered before the end of surgery.

Methods: After IEC approval, a prospective, randomized, double blinded study was conducted on 60 ASA I and II adult patients undergoing elective colorectal surgery under general anaesthesia. Patients were randomly divided into two groups of 30 patients in each group: Group O and Group G. Patients of Group O received 100 mcg/Kg ondansetron and Group G received 40mcg/Kg Granisetron Intravenously 20 minutes before the end of surgery. The patients were observed for 24 hours for PONV and other possible adverse events. Postoperative pain intensity was determined using a 10-cm visual analogue scale. Four-point satisfaction scores were determined at 24 hours.

Results: Sixty patients participated in the study. Demographic characteristics and operative data were similar in both groups. The only adverse event reported by patients during the 24-hour observation period was nonsevere headache. The number of patients experiencing headache was similar in group O and group G. There were no significant differences between group O and group G in the incidence of PONV, patient satisfaction, or adverse events.

Conclusions: Patients administered ondansetron 100 mcg/kg or granisetron 40 mcg/kg 20 minutes before the end of Middle ear surgery had good PONV control during the 24-hour postoperative observation period. However, there were no significant differences between the group O and group G in the incidence of PONV, patient satisfaction, or adverse events.

Key words: Middle Ear Surgery, postoperative nausea and vomiting, ondansetron, granisetron.

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I. Introduction

Postoperative nausea and vomiting (PONV) is a common problem among patients undergoing surgery as the incidence varies from 30% to as high as 80% in various surgical procedures [1–3]. Furthermore, PONV is a contributor to increased post-anesthesia care unit (PACU) length of stay, increased hospital costs, and decreased patient satisfaction [4,5]. Risk factors for PONV include sex, history of PONV or motion sickness, smoking status, age, anesthesia type, duration of anesthesia, use of volatile anesthetics including nitrous oxide, type of surgery, and opioid use. Because patient physiology and surgical type cannot be changed, current guidelines and strategies focus on the alteration of the anesthetic plan to help decrease the incidence of PONV, including the reduction or exclusion of opioids and volatile anesthetic agents [1,3]. Additionally, the use of

prophylactic antiemetics administered preoperatively or intraoperatively is a common strategy to reduce PONV. Among the most commonly used antiemetics are 5-HT₃ antagonists such as ondansetron, steroids such as dexamethasone, neurokinin antagonists such as aprepitant, phenothiazine antipsychotics such as perphenazine, and anticholinergic pharmacotherapy such as scopolamine. Although it is known that the use of antiemetics is effective at preventing PONV, controversy exists regarding the best antiemetics for prevention. For PONV prophylaxis, both ondansetron and granisetron have been recommended to be administered at the start of anesthesia.[6,7] However, other studies have found that antiemetic prophylaxis with these drugs was more efficient when they were administered at the end of surgery. [8] The aim of the present study was to investigate the antiemetic prophylactic effect of ondansetron and granisetron administered before the end of surgery to patients undergoing elective colorectal surgery.

II. Materials And Methods

Ethical statement:The study was approved by the Institutional Ethics Committee, Patna Medical College & Hospital, Patna, Bihar, India. Informed written consent was obtained after informing the participants about the nature, scope and risks related to the study.

Study location :The study was carried out in the Department of Anaesthesiology, Patna Medical College & Hospital, Patna, Bihar., India.

Study population:Patients came for Middle Earsurgery under general anaesthesia to operation theatre in the Department of Anaesthesiology,Patna Medical College & Hospital, Patna, Bihar, India.

Study design :It a prospective, randomized double blind, comparative study.

Sample size estimation with two means study^{7,8}:

Then the total sample size for the study is as follows

Where

Z_{α} is the normal deviate at a level of significance (Z_{α} IS 1.96 for 5% level of significance)

$Z_{1-\beta}$ is the normal deviate at (1- β)% power with β % of type II error (0.84 at 80% power of study)

$r = n_1 / n_2$ is the ratio of sample size required for 2 groups

δ is standard deviation ,d is difference of means of 2 groups .

The total sample size for the study with $r = 1$ (equal sample size)

The values are obtained from previous study .

Taking the α at 5% and desired power of study as 80%

We will accept a $p < 0.05$ as significant. We mean that we are ready to accept that the probability that the result is observed due to chance is 5%

Confidence level = 95%

Confidence interval = 5.22

Sample size = 30

find the smallest sample sizes required to achieve a fixed margin of error, using simple random sampling.

Therefore ,

$$n = \{(r+1) (Z_{\alpha/2} + Z_{1-\beta}) \delta^2 \} / r d^2$$

$$n = (1+1) (1.96+0.84)^2 (10.366)^2 / 1 * (19.29 - 12.8)^2 = 1684.878 / 42.12 = 40.112 \approx 40$$

The total sample size required for the study 60, each group contain 30 patients

(total population = 120)

Study duration :One and half years (October-2018 to April-2019)

Inclusion Criteria : In patient with

1. Informed written consent.
2. ASA grade I and II posted for elective surgery under general anaesthesia
3. Age group 18 -60 years.
4. Weight 45-65 kg

Exclusion Criteria:

1. Patient refusal
2. Hypertension (controlled and uncontrolled both)
3. Systolic blood pressure less than 90 mm Hg
4. Heart rate less than 60 beats/ min.
5. Coronary artery disease
6. COPD
7. Morbid obesity
8. Diabetes Mellitus

9. Renal compromise
10. Pregnant and lactating women
11. Menstruating patient
12. History of motion sickness
13. Those who were receiving drugs with known antiemetic effects

Study group: The study was carried out on 60 normotensive patients of age group 18 to 60 years of ASA class 1 and 2 posted for elective colorectal surgery under general anaesthesia.

Besides a long and thorough clinical examination like history, general examination and systemic examination the investigations a blood haemoglobin, total count and differential count of WBC, ESR, Routine & microscopic examination of urine, ECG, X-Ray chest PA view, blood sugar –fasting and postprandial, Blood urea, serum creatinine were be done to exclude any systemic illness and also for ASA grading.

Premedication: All the patients will be pre-medicated with oral tab. Rantidine 150 mg and tab. Alprazolam 0.25 mg on the night before surgery. All the patients will remain fasting for overnight for 8 hours prior to surgery.

Intervantion plan: On arrival in the operation theatre, routine monitoring in the form of ECG (lead II and V₅), respiration, NIBP and SPO₂ were instituted. Intravenous access was established with 18G intravenous catheter on the dorsum of the non -dominant hand and infusion of lactated Ringer's solution was started.

By use of computer generated random numbers, Patients were randomly allocated in one of any two groups of 30 each.

Group O :- Patients of group O received 100Mcg/Kg Ondasetron.

Group G :- Patients of group G received 40 Mcg/Kg Granisetron.

Study drugs were diluted in 10 ml of normal saline for blinding and given intravenously 20 minutes before the end of surgery.

The patients' lungs were pre-oxygenated with 100 % Oxygen for 2 min. Two minutes after preoxygenation (t = 120s), the study drug was administered intravenously over 30 seconds. Anaesthesia was then induced (t = 150s) with inj. Pentazocine 0.5 mg per kg body weight and inj. Propofol was given slowly upto loss of eye reflexes. All the groups were received inj. Vecuronium 0.1mg/kg body weight for facilitation of intubation of trachea. The patients' lungs were then ventilated with Sevoflurane 1% and nitrous oxide 50% in oxygen, maintaining end-expiratory carbon dioxide tension at 4.0±4.5 kPa. Four minutes later (t = 390 s), laryngoscopy was done using standard Macintosh blade. Oral Intubation was done with appropriate sized, disposable, high volume low pressure, portex cuffed endotracheal tube within 30 seconds. Anaesthesia was maintained with O₂, N₂O, Sevoflurane and inj. Vecuronium top up. At the end of surgery anaesthesia was reversed with inj. Neostigmine 0.05 mg/kg and inj. Glycopyrrolate 0.2mg per mg of Neostigmine intravenously. Patients were shifted to recovery room after adequate reversal and monitored for vital parameters postoperatively.

Rescue interventions: Rescue interventions were planned for bradycardia and hypotension. Bradycardia (<50 BPM) was treated with atropine and hypotension (<20% of baseline value) was treated with mephenteramine.

Blinding: Both the patient and the anaesthesiologist who administered the general anaesthesia and recorded the data, were blinded to the study group. An independent anaesthesiologist prepared and administered the study drugs.

Parameter of observation: All patients were observed in the recovery room during the first postoperative hour and then in the ward by the same investigator.) who was blinded to the treatment groups. The investigator determined nausea vomiting scores (0 = no nausea, 1 = nausea, 2 = retching and/or 1 vomitus, 3 = >1 vomitus) by direct questioning of the patients at the following postoperative times: 0 (when the patient first responded to a simple verbal order) and 1, 2, 4, 8, 12, and 24 hours. Patients with a PONV score of ≥ 2 received metoclopramide 10 mg IV as a rescue antiemetic. The investigator also assessed postoperative pain intensity using a 10-cm visual analogue scale (VAS) (0 = no pain to 10 = the worst pain). At 24 hours, the investigator recorded rescue antiemetic drug use, complete or incomplete response, total fentanyl consumption, and degree of satisfaction (1 = very unsatisfied, 2 = unsatisfied, 3 = satisfied, 4 = very satisfied). Complete response was defined as no PONV and/or no need for the rescue antiemetic drug. Heart rate (per minute), Systolic blood pressure (mm of Hg), Diastolic blood pressure (mm of Hg), Mean arterial pressure (mm of Hg) and SpO₂ were observed

Statistical analysis: All the data would be selected randomly and tabulated, and then analyzed with appropriate statistical tools "MedCalc". Data will be presented as mean with standard deviation or proportions as appropriate. Mean, median, standard deviation and variance would be calculated. Student's paired T-test, Chi – square Test, Student t-test, and Analysis of variance would be applied for statistical analysis.

III. Results

Sixty patients were included in the study. There were 30 patients in each group, and all of the patients completed the study. There were no significant differences between the two groups in regard to demographic characteristics, mean duration of surgery, mean duration of anesthesia, or intraoperative total fentanyl consumption (Table I). The only adverse event was reported by patients during the 24-hour observation period was nonsevere headache. The number of patients experiencing headache was similar in group O and group G (6 [20%], and 10 [33%] patients, respectively). All patients had postoperative pain scores ranging from 0 to 5 on the VAS. No differences were found in mean pain scores or postoperative total mean fentanyl consumption between both groups (Table II).

Table I. Baseline demographic characteristics and operative data in adult patients undergoing Middle Ear surgery (N = 60). * Data are mean (SD) unless otherwise noted.

Variable	Group O(n=30)	Group G(n=30)	P -value
Age(years)	49.1 (4.8)	47.6 (9.3)	0.09
Weight(Kg)	72.1(10.10)	70.8(8.8)	0.12
Height(cm)	165.3(8.9)	163.9(7.7)	0.08
male	21	23	0.78
Female	9	7	0.56
Duration of surgery(minutes)	267(18.9)	271(17.8)	0.08
Duration of Anaesthesia(minutes)	297(21.8)	298(19.9)	0.07
Intraoperative fentanyl use(mcg)	289(34.9)	285(35.8)	0.09

Table II. Postoperative data in adult patients undergoing Middle Ear surgery (N = 60).

Variable	Group O	Group G	P value
Fentanyl(mcg)	107.8 (23.7)	112 (21.6)	0.09
Rescue antiemetic, no (96)	8 (20)	7(18)	0.080
Complete response no (96)	21(50)	23 (47)	0.12
Satisfaction score*	3 (2-4)	3 (2-4)	0.09
Headache, no (96)	6 (20)	10 (33)	0.12

*Scale: 1 = very unsatisfied; 2 = unsatisfied; 3 = satisfied; 4 = very satisfied.

The mean (SD) satisfaction scores in group O and group G (3.0 [0.4] and 3.0 [0.6], respectively) were statistically not significant.

Table III. The incidence and severity of postoperative nausea and vomiting in adult patients undergoing Middle Ear Surgery (N -- 90).

Postoperative Hour	Ondasetron Group (n=30)		Granisetron Group (n=30)	
	No (%)	Score* mean (SD)	No (%)	Score* mean (SD)
0	8(30)	0.6(0.9)	7 (23)	0.4 (0.8)
1	2(7)	0.1 (0.4)	8(19)	0.3(0.5)
2	0	0	0	0
4	0	0	0	0
8	0	0	0	0
12	0	0	0	0
24	0	0	0	0

Immediately after surgery (period 0), more patients in the group O had PONV compared with the group G but statistically not significant. This result remained almost same during 24 hours follow up period (Table III).

IV. Discussion

PONV are observed with all types of surgery and in all patient populations when prophylactic antiemetic drugs are not used.[6] The prevalence of PONV in patients undergoing Middle Ear surgery without antiemetic prophylaxis ranges from 43% to 72%. [9,10] In many studies, the prevalence of PONV has been found to decrease significantly with antiemetic prophylaxis.[11,12] Traditional antiemetic drugs (eg, droperidol and metoclopramide) may be associated with adverse events like sedation, dry mouth, and extrapyramidal symptoms. The 5-HT₃ receptor antagonists are not associated with such adverse events, and they have more effective antiemetic activity. [9] Therefore, 5-HT₃ receptor antagonists are used to prevent and treat PONV

after a variety of surgical procedures.[6] Ondansetron, the first selective 5-HT₃ receptor antagonist used for the prevention of PONV, and granisetron, another selective 5-HT₃ receptor antagonist, have been found to be well tolerated and highly effective in preventing and treating PONV.[10] The timing of prophylactic antiemetic management might be important. In some studies, ondansetron and granisetron were administered at the start of anesthesia for PONV prophylaxis.[7] However, 1 study found it was more effective to administer ondansetron 4 mg IV at the end of surgery than at the start of anesthesia (complete responses, 74% and 71%, respectively; $P < 0.05$). [8] Administering these antiemetic drugs at the end of surgery had additional benefits, including increased effectiveness of lower doses and greater patient satisfaction.[8] Ondansetron reaches peak plasma concentration in 20 to 30 minutes after intravenous administration.[7] In healthy volunteers, granisetron has also been shown to reach peak plasma concentrations 30 minutes after intravenous administration. [7] Therefore, intravenous administration of either drug 20 to 30 minutes before extubation may provide sufficient postoperative antiemetic effect. However, ondansetron and granisetron may not be sufficiently effective when administered at the end of surgery or just before extubation. So et al found that patients administered a single 4-mg dose of IV ondansetron at the end of Laproscopic cholecystectomy (just before tracheal extubation) had similar PONV scores to the placebo group at the end of the study.[13] The authors concluded that ondansetron 4 mg after surgery did not reduce the prevalence of nausea and vomiting. Quaynor and Raeder administered patients IV metoclopramide 20 mg or ondansetron 8 mg after surgery.[14] Despite the high doses, the overall prevalence of PONV was high (47% with metoclopramide and 43% with ondansetron). In both studies, the high rate of PONV might be attributed to the delay in the administration of antiemetic drugs. Because the mean (SD) plasma elimination $t_{1/2}$ of both ondansetron and granisetron are relatively short (-2.8 [0.6] and -3.1 [1.2] hours, respectively), [15,16] patients may need to receive a repeat dose. However, for short surgical procedures, these drugs may be administered during anesthesia induction. In the present study, No significant differences were found between the groups in the risk factors for PONV (eg, patient demographic characteristics, operative procedure, anesthesia administration procedure, anesthetics used, and intraoperative and postoperative analgesic consumption). Therefore, we believe that the differences in PONV control observed were associated with the antiemetic drugs used. The adult dose of ondansetron recommended to prevent PONV is 4 mg.[7] However, in a randomized, double-blind, placebo-controlled study of 2119 patients (aged >12 years), Kovac et al[17] found that the 4-mg dose of ondansetron was not effective. In a meta-analysis of 53 trials with 7177 patients receiving 24 different ondansetron formulations, Tramer et al[18] recommended IV ondansetron 8 mg for PONV prophylaxis. In a randomized, double-blind comparison study by Zarate et al, [18] outpatients undergoing otolaryngologic procedures received IV ondansetron 4 or 8 mg <30 minutes before the end of surgery. The 8-mg dose was not found to be significantly more effective than ondansetron 4 mg. The ondansetron dose used in the present study was within the recommended range (4-8 mg) for PONV prevention.

To prevent PONV after various surgical procedures, the optimal dose of granisetron was found to be 40 mcg/kg[9,19]; higher doses have not been found to be more effective.[19] Similarly, granisetron 40 mcg/kg was found to be the minimum effective dose for preventing PONV in patients undergoing colorectal surgery. [10] Therefore, granisetron 40 mcg/kg was used in this study. In our study we found that antiemetic effects of ondansetron and granisetron in PONV found no difference in effectiveness between the 2 drugs. A dose of IV granisetron 3 mg was found to provide no more effective antiemetic prophylaxis than ondansetron 4 mg in patients undergoing Middle Ear surgery. A 2003 study found granisetron to be superior to ondansetron in the prevention of PONV after outpatient gynecologic laparoscopic surgery (administered 2 minutes before induction of general anesthesia); granisetron 2 mg IV was found to be more effective than ondansetron 4 mg IV (emetic episodes were observed in 7% of patients who had received intravenous granisetron and 20% in those who had received ondansetron).[20] In the study by Naguib et al, a dose of IV granisetron 3 mg was comparable to ondansetron 4 mg with regard to effective antiemetic prophylaxis in patients undergoing Laproscopic cholecystectomy. The result of this study is similar to our study.

V. Conclusions

Patients administered ondansetron 100 mcg/kg or granisetron 40 mcg/kg 20 to 30 minutes before the end of Middle Ear surgery had significantly higher PONV control during the 24-hour postoperative observation period. However, there were no significant differences between group O and group G in the prevalence of PONV, patient satisfaction, or adverse effects. The main limitation of our study is small sample size.

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