ORIGINAL RESEARCH

A randomized trial evaluating the effectiveness of ondansetron for postoperative nausea and vomiting in ophthalmic surgeries

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Abstract

Aim: To determine the efficacy of intravenous ondansetron in the prevention of postoperative nausea and vomiting (PONV) in patients undergoing ophthalmic surgeries under general anesthesia.

Materials and methods: Five hundred patients, receiving endotracheal anesthesia were randomized either to no drug (group I, n=250) or single dose, intravenous ondansetron just prior to induction (group IIa, n=125) or prior to reversal at the conclusion of surgery (group IIb, n=125).

Results: In the first 24 hours postoperatively, the incidence of nausea and vomiting was 20% and 47.2% respectively in control group I, 23.3% and 42.4% in group IIa, and 5.6% and 31.2% in group IIb (p=0.001,0.003). The mean number of nausea and vomiting episodes per patient declined significantly in group IIb, compared to the controls (p=0.001, 0.004). No differences were observed in group IIa.

Conclusion: Ondansetron administered intravenously at the conclusion of ophthalmic surgery reduces the occurrence of postoperative nausea and vomiting.

Key words: Ondansetron, Postoperative nausea and vomiting, Randomized trial

Introduction

Despite significant advances in the delivery of general anesthesia, postoperative nausea and vomiting (PONV) remains a troublesome concomitant phenomenon and is described as "the big 'little problem' for surgical patients".[1] Vomiting after surgery can delay discharge or lead to unanticipated hospital admission, thus increasing costs.[2,3] Ondansetron, a hydroxytryptamine subtype 3 (5-HT_3) receptor antagonist, has been shown to be highly effective in the prevention and treatment of PONV in both adults and children.[4-6] However, barring strabismus surgery,[7,8] the role of ondansetron in preventing PONV in patients undergoing various ophthalmic surgeries under general anesthesia has not been examined. Further, no information is available comparing the efficacy of administering ondansetron prior to the induction of anesthesia with that prior to the reversal of anesthesia at the end of surgery. We therefore conducted a randomized, controlled clinical trial to elucidate the efficacy of single dose intravenous ondansetron in patients undergoing ophthalmic surgeries under general anesthesia.

Materials and methods

The study was approved by the institutional review board The sample size was 250 each, for the control group (group I)

and treated group (group II), and was calculated by assuming the incidence of PONV to be 30%, alpha = 0.05, power of the test 90% and the risk ratio = 1.5. In group II, the first 125 patients (group IIa) received ondansetron just prior to the induction of anesthesia and the remaining 125 patients (group IIb), received the study drug just prior to reversal, at the end of the procedure.

Randomization was done using computer generated random numbers. Informed consent was obtained from all eligible patients. Exclusion criteria included: patients who had vomited or received antiemetics within 24 hours prior to surgery, pregnant and breast feeding women, patients who were on long-term systemic corticosteroids and children less than four years of age. All females of childbearing age were tested for pregnancy as the safety of the drug in pregnant women is yet to be established. Patients randomised to group II, received 4 mg ondansetron hydrochloride diluted in 20 ml normal saline and infused intravenously over 2 to 5 minutes immediately prior to the induction (group IIa) or reversal (group IIb) of anesthesia.

Preoperatively, patients fasted for a minimum of five hours. Premedication included intramuscular injection of pentazocine hydrochloride 0.6-mg/kg body weight (maximum dose 30.0 mg) and atropine sulfate 0.02-mg/kg body weight (maximum dose 0.6 mg). In children between 4 and 7 years of age, oral trichlorphos sodium 50-70 mg/kg body weight was administered.

Anesthesia was induced using either thiopentone sodium (5-7 mg/kg body weight) and succinylcholine chloride (1-2 mg /kg body weight), or thiopentone sodium and a non-depolarizing muscle relaxant vecuronium, or pancuronium (0.08 - 0.1mg/ kg body weight), or halothane/isoflurane and 50% nitrous oxide in oxygen *via* mask. The technique of induction of general anesthesia was chosen according to the discretion of the anesthetist. Ventilation was either spontaneous or controlled. Anesthesia was maintained with nitrous oxide and oxygen, and supplemented when necessary with volatile anesthetic agents such as halothane or isoflurane 0.5 - 1.5%. Pentazocine hydrochloride was used as an intraoperative analgesic when required. Nitrous oxide was discontinued if the surgeon decided to inject intravitreal expansile gas such as sulfur hexafluoride (SF_6) or perfluropropane (C_3F_8). At the conclusion of the procedure, residual neuromuscular blockade was antagonized with the injection of neostigmine methyl sulfate (0.04 mg/kg body weight) and atropine sulfate (0.02 mg/kg body weight). Tracheal extubation was performed after the restoration of reflexes, with the patient fully awake. In the post-anesthetic care unit, vital signs were monitored for three hours.

Outcome variables, nausea and vomiting, were noted 0 - 24 hours postoperatively by a masked observer. Nausea was defined as a subjective feeling of the urge to vomit, and vomiting as the forceful expulsion of gastric contents from the mouth. For the purpose of this study, retching was not considered emesis. Each episode had to be separated by a minute before being considered as a distinct episode. A complete response was defined as no episode; a minor response as one episode; a major response as two episodes; and treatment failure as more than two episodes or the receipt of ondansetron as a rescue antiemetic.

Statistical analysis

Categorical variables were analysed by Chi-square test, and Fisher's exact test. Incidence of nausea or vomiting and the number of episodes per person during 0-24 hour postoperative period were tested by Mantel-Haenszel test and Mann-Whitney U-test respectively. Statistical tests were considered significant if the p values were less than or equal to 0.05.

Results

Demographics

There were no significant differences between controls (group I) and cases (group IIa and group IIb) with respect to patient age, gender, weight, ASA status, previous anesthetic experience, number of days since last menstrual cycle, and history of motion sickness (**Table 1**). Also, no differences were noted between the groups in the types and duration of anesthesia and the types of surgical procedures. Various ophthalmic surgeries performed in this study included: penetrating keratoplasty, lensectomy, membranectomy, wound repair and anterior chamber reconstruction, strabismus, trabeculectomies, evisceration, enucleation, oculoplastic, scleral graft, choroidal tap, removal of infected scleral buckle, cataract extraction and pars plana vitrectomy with or without scleral buckling.

Efficacy

There was no difference in the incidence of postoperative nausea and vomiting between group I and group IIa; however, a significant reduction in the incidence of PONV occurred in group IIb compared to group I (**Table 2**). In addition, in group IIb, the administration of ondansetron significantly reduced the mean number of nausea and emetic episodes per patient as compared to that in group I (**Table 3**). A complete response to nausea and vomiting was achieved in 94.4% and 68.8% of subjects in group IIb compared to 80% ($p = 0.005$) and 52.8% ($p=0.006$) respectively in group I (**Fig. 1** and **2**).

Comparing the combined analysis of group IIa and IIb with group I (**Table 2** and **3**), the incidence and mean number of emetic episodes per patient were significantly lower in patients receiving ondansetron. No such differences were noted in the occurrence of postoperative nausea.

Predictors of complete response

The influence of various pre- and intraoperative variables on complete response to PONV was analysed. No factor was correlated to the occurrence of postoperative nausea. However, a significantly higher complete response to postoperative vomiting was noted in males ($p = 0.037$) and in patients undergoing posterior segment surgeries without buckling ($p = 0.049$) (**Fig. 3** and **4**).

Table 1. Demographic data

	Group I n =250 (%)	Group II n =250 (%)	P	Group IIa n =125 (%)	P	Group IIb n =125 (%)	P
Age (in years)	35.3±17.83	34.89±18.40	0.794	34.64±18.53	0.733	35.14±18.35	0.931
Sex Male Female	 185 (74.0) 65 (26.0)	 198 (79.2) 52 (20.8)	 0.169	 99 (79.2) 26 (20.8)	 0.268	 99 (79.2) 26 (20.8)	 0.268
Weight (in kg)	53.61±15.66	54.67±15.91	0.451	53.82±15.36	0.961	55.52±16.46	0.281
ASA Grade I II III	 65 (26.0) 173 (69.2) 12 (4.8)	 59 (23.6) 177 (70.8) 14 (5.6)	 0.783	 27 (21.6) 92 (73.6) 6 (4.8)	 0.642	 32 (25.6) 85 (68.0) 8 (6.4)	 0.809
Previous anesthetic experience Nausea Vomiting	116 (46.4) 15 (12.9) 32 (27.6)	112 (44.8) 17 (15.2) 33 (29.5)	0.719	60 (48.0) 10 (16.7) 18 (30.0)	0.769	52 (41.6) 7 (13.5) 15 (28.9)	0.378
Number of days since last menstrual cycle	11.03±5.53	12.85±8.79	0.369	14.47±9.45	0.209	10.64±7.66	0.877
History of motion sickness	7 (2.8)	6 (2.4)	1.00	4 (3.2)	0.287	2 (1.6)	0.375
Types of anesthesia Spontaneous Controlled	 91 (36.4) 159 (63.6)	 81 (32.4) 169 (67.6)	 0.347	 39 (31.2) 86 (68.8)	 0.319	 42 (33.6) 83 (66.4)	 0.593
Duration of anesthesia (in hours)	2.32±0.89	2.45±0.93	0.116	2.47±0.97	0.140	2.42±0.88	0.290
Types of surgery Anterior Posterior without buckle Posterior with buckle Others	 15 (6.0) 70 (28.0) 144 (57.6) 21 (8.4)	 22 (8.8) 72 (28.8) 137 (54.8) 19 (7.6)	 0.653	 13 (10.4) 33 (26.4) 69 (55.2) 10 (8.0)	 0.505	 9 (7.2) 39 (31.2) 68 (54.4) 9 (7.2)	 0.853

Table 2. Efficacy -- Incidence of nausea and vomiting

* Chi-square test $ Fisher's Exact test

	Group I n =250 (%)	Group II n =250 (%)	P*	Group IIa n =125 (%)	P*	Group IIb n =125 (%)	P*
Intraoperative vomiting	11 (4.4)	17 (6.8)	0.243	11 (8.8)	0.087	6 (4.8)	0.861
Postoperative nausea	50 (20.0)	36 (14.4)	0.097	29 (23.2)	0.474	7 (5.6)	<0.001
Postoperative vomiting	118 (47.2)	92 (36.8)	0.019	53 (42.4)	0.378	39 (31.2)	0.003
Rescue antiemetic	6 (2.4)	8 (3.2)	0.467	5 (4.0)	0.119	3 (2.4)	0.349$

Table 3. Mean number of episodes per patient

* Mann-Whitney U-test

	Group I n =250	Group II n =250	P*	Group IIa n =125	P*	Group IIb n =125	P*
Nausea	0.34±0.85 (0 - 6)	0.28±0.78 (0 - 6)	0.136	0.45±0.95 (0 - 5)	0.369	0.11±0.51 (0 - 3)	<0.001
Vomiting	1.26±1.71 (0 - 6)	0.94±1.57 (0 - 6)	0.013	1.04±1.58 (0 - 6)	0.246	0.84±1.55 (0 - 6)	0.004

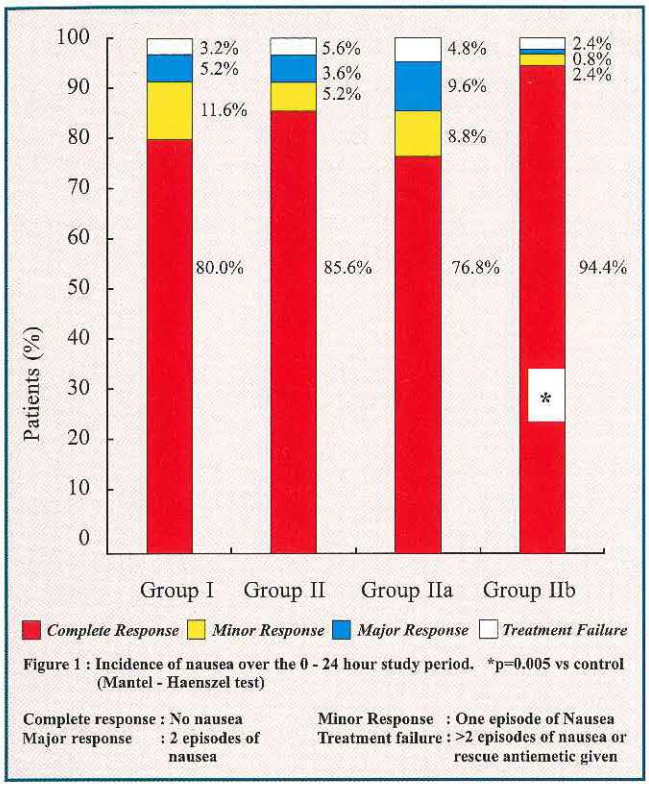

Figure 1 : Incidence of nausea over the 0 - 24 hour study period. *p=0.005 vs control (Mantel - Haenszel test)

Complete response : No nausea
Minor Response : One episode of Nausea
Major response : 2 episodes of nausea
Treatment failure : >2 episodes of nausea or rescue antiemetic given

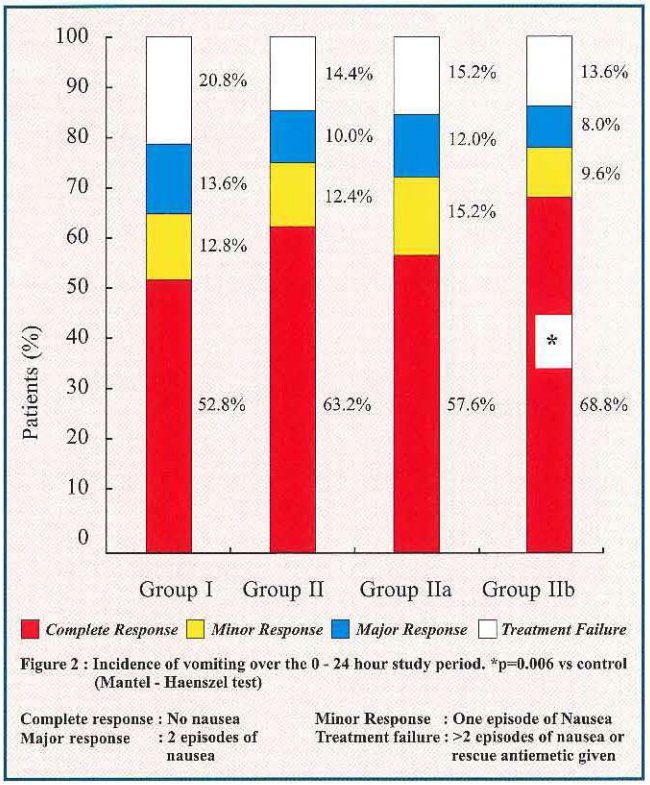

Figure 2 : Incidence of vomiting over the 0 - 24 hour study period. *p=0.006 vs control (Mantel - Haenszel test)

Complete response : No nausea
Minor Response : One episode of Nausea
Major response : 2 episodes of nausea
Treatment failure : >2 episodes of nausea or rescue antiemetic given

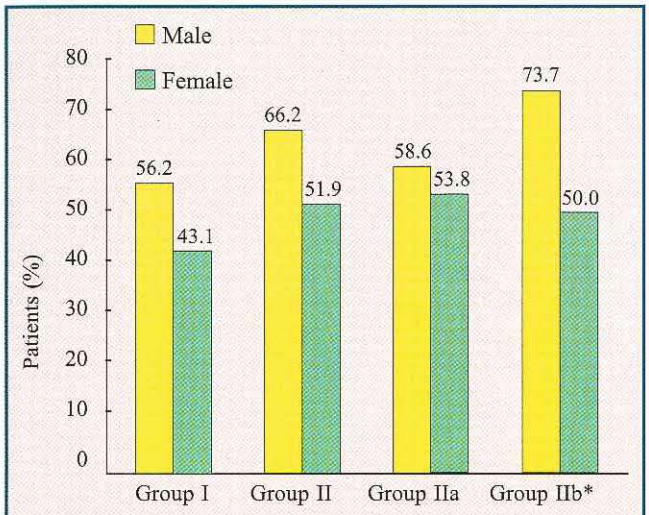

Figure 3 : Comparison of complete response of vomiting between male and female population. * p = 0. 037 (Chi-square test)

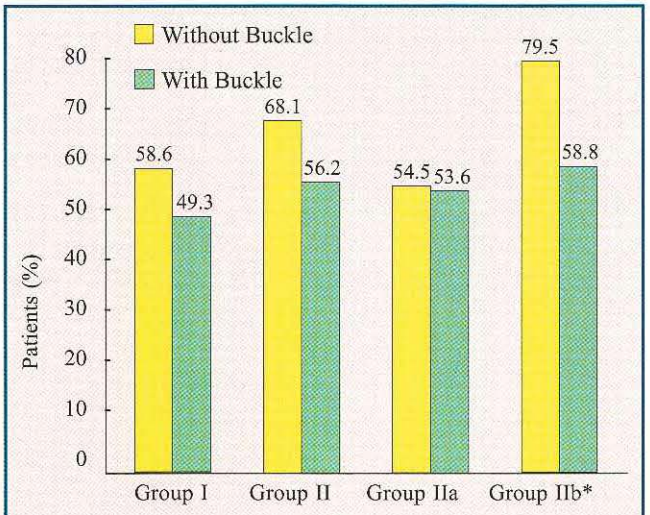

Figure 4 : Comparison of complete response of vomiting in patients with or without buckling. * p = 0. 049 (Chi-square test)

Discussion

This study indicates that intravenous ondansetron is more effective in preventing PONV if given prior to the reversal of anesthesia at the end of the procedure than if administered prior to the induction of anesthesia. Not only does it reduce the incidence of PONV, but it also decreases the mean number of episodes per patient. The pooled data of cases (groups IIa and IIb) also confirms the antiemetic property of ondansetron.

The vomiting reflex is a multifactorial phenomenon mediated by serotonergic transmission. The aetiology of PONV is complex and is dependent on patient characteristics, type of surgery, anesthetic techniques and postoperative course.[9] The efficacy of ondansetron in the treatment of PONV in various ophthalmic surgeries including retinal detachment surgery with or without vitrectomy has not been reported earlier. This study confirms the superiority of the drug in male patients and in those patients undergoing posterior segment surgeries without buckling. Most investigators have reported a significantly lower incidence of PONV in male adults compared to female adults.[10,11] However, the gender difference is not noted in the preadolescent age group or in patients beyond the eighth decade of life, suggesting that variations in serum gonadotropin levels may be responsible for the higher incidence of emesis in women.[12,13]

Patients who undergo either scleral buckling or combined vitrectomy and scleral buckling require extensive manipulation of all the rectus muscles during surgery in contrast to patients who undergo either strabismus surgery or vitrectomy without buckling. The reduced manipulation of recti could be the reason for a more complete response to emesis in patients undergoing posterior segment surgeries without buckling.

Although ondansetron decreased the overall incidence of PONV in group IIb (drug administered prior to reversal), there were no significant differences between group I (controls) and group IIa (drug administered prior to induction). Because of the relatively short half-life of ondansetron (3.5 hours),[14] it is possible that administering the drug at the end of the procedure is more effective as prophylaxis against PONV in the ophthalmic population. Considering the fact that 31% of patients in group IIb did have postoperative vomiting, it may be prudent to repeat the drug after 3-4 hours in case of high risk individuals.

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