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 hydroxtryptamin 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 antiemtics 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 sulphate 0.02-mg/kg body weight (maximum dose 0.6 mg). In children between 4
and 7 years of age, oral trichlorophos 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
(0.08-0.1 mg/kg body weight), or halothane/isofluurane 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
isofluurane 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 (SF6) or
perfluoropropane (C3F8). 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
c 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
ewmetic 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

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group IIa</th>
<th>Group IIb</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n = 250 (%)</td>
<td>n = 250 (%)</td>
<td>n = 125 (%)</td>
<td>n = 125 (%)</td>
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<tr>
<td>Age (in years)</td>
<td>35.3±17.83</td>
<td>34.89±18.40</td>
<td>34.64±18.53</td>
<td>35.14±18.35</td>
<td>0.931</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>185 (74.0)</td>
<td>198 (79.2)</td>
<td>99 (79.2)</td>
<td>99 (79.2)</td>
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<tr>
<td>Female</td>
<td>65 (26.0)</td>
<td>52 (20.8)</td>
<td>26 (20.8)</td>
<td>26 (20.8)</td>
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<tr>
<td>Weight (in kg)</td>
<td>53.61±15.66</td>
<td>54.67±15.91</td>
<td>53.82±15.36</td>
<td>55.52±16.46</td>
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<td>ASA Grade</td>
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<tr>
<td>I</td>
<td>65 (26.0)</td>
<td>173 (69.2)</td>
<td>116 (46.4)</td>
<td>85 (68.0)</td>
<td>0.809</td>
</tr>
<tr>
<td>II</td>
<td>12 (4.8)</td>
<td>14 (5.6)</td>
<td>12 (4.8)</td>
<td>8 (6.4)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>116 (46.4)</td>
<td>173 (69.2)</td>
<td>12 (4.8)</td>
<td>8 (6.4)</td>
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<tr>
<td>Previous anesthetic experience</td>
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<tr>
<td>Nausea</td>
<td>116 (46.4)</td>
<td>173 (69.2)</td>
<td>12 (4.8)</td>
<td>8 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>116 (46.4)</td>
<td>173 (69.2)</td>
<td>12 (4.8)</td>
<td>8 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Number of days since last menstrual cycle</td>
<td>11.03±5.53</td>
<td>12.85±8.79</td>
<td>10.64±7.66</td>
<td>11.04±7.66</td>
<td>0.877</td>
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<tr>
<td>History of motion sickness</td>
<td>7 (2.8)</td>
<td>6 (2.4)</td>
<td>4 (3.2)</td>
<td>2 (1.6)</td>
<td>0.375</td>
</tr>
<tr>
<td>Types of anesthesia</td>
<td></td>
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<td></td>
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<tr>
<td>Spontaneous</td>
<td>91 (36.4)</td>
<td>81 (32.4)</td>
<td>39 (31.2)</td>
<td>42 (33.6)</td>
<td>0.593</td>
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<tr>
<td>Controlled</td>
<td>159 (63.6)</td>
<td>169 (67.6)</td>
<td>86 (68.8)</td>
<td>83 (66.4)</td>
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<tr>
<td>Duration of anesthesia (in hours)</td>
<td>2.32±0.89</td>
<td>2.45±0.93</td>
<td>2.47±0.97</td>
<td>2.42±0.88</td>
<td>0.290</td>
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<td>Types of surgery</td>
<td></td>
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<tr>
<td>Anterior</td>
<td>15 (6.0)</td>
<td>22 (8.8)</td>
<td>13 (10.4)</td>
<td>9 (7.2)</td>
<td>0.853</td>
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<tr>
<td>Posterior without buckle</td>
<td>70 (28.0)</td>
<td>72 (28.8)</td>
<td>33 (26.4)</td>
<td>39 (31.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior with buckle</td>
<td>144 (57.6)</td>
<td>137 (54.8)</td>
<td>69 (55.2)</td>
<td>68 (54.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Others</td>
<td>21 (8.4)</td>
<td>19 (7.6)</td>
<td>10 (8.0)</td>
<td>9 (7.2)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Efficacy — Incidence of nausea and vomiting

<table>
<thead>
<tr>
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<td>n = 125 (%)</td>
<td>n = 125 (%)</td>
<td></td>
</tr>
<tr>
<td>Intraperative vomiting</td>
<td>11 (4.4)</td>
<td>17 (6.8)</td>
<td>11 (8.8)</td>
<td>6 (4.8)</td>
<td>0.861</td>
</tr>
<tr>
<td>Postoperative nausea</td>
<td>50 (20.0)</td>
<td>36 (14.4)</td>
<td>29 (23.2)</td>
<td>7 (5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative vomiting</td>
<td>118 (47.2)</td>
<td>92 (36.8)</td>
<td>53 (42.4)</td>
<td>39 (31.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Rescue antiemetic</td>
<td>6 (2.4)</td>
<td>8 (3.2)</td>
<td>5 (4.0)</td>
<td>3 (2.4)</td>
<td>0.349</td>
</tr>
</tbody>
</table>

### Table 3. Mean number of episodes per patient

<table>
<thead>
<tr>
<th></th>
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<td>n = 250 (%)</td>
<td>n = 125 (%)</td>
<td>n = 125 (%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>0.34±0.85 (0 - 6)</td>
<td>0.28±0.78 (0 - 6)</td>
<td>0.136</td>
<td>0.45±0.95 (0 - 5)</td>
<td>0.369</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.26±1.71 (0 - 6)</td>
<td>0.94±1.57 (0 - 6)</td>
<td>0.013</td>
<td>1.04±1.58 (0 - 6)</td>
<td>0.246</td>
</tr>
</tbody>
</table>
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 etiology of PONV is complex and is dependent on patient characteristics, type of surgery, anesthetic techniques and postoperative course. 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. 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.
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), 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.