Ramosetron compared with granisetron for the prevention of vomiting following strabismus surgery in children

Yoshitaka Fujii, Hiroyoshi Tanaka, Mutsuko Ito

Abstract

Background/aims—Postoperative vomiting occurs frequently after strabismus surgery in children. Granisetron, a selective 5-hydroxytryptamine type 3 receptor antagonist, is effective for the prevention of vomiting following paediatric strabismus surgery. Ramosetron, another new antagonist of 5-hydroxytryptamine type 3 receptor, has more potent and longer acting properties than granisetron against cisplatin induced emesis. This study was undertaken to compare the efficacy and safety of granisetron and ramosetron for the prevention of vomiting following strabismus surgery in children.

Methods—In a randomised, double blinded manner 80 children, aged 4–10 years, received intravenously granisetron 40 µg/kg or ramosetron 6 µg/kg (n=40 each) at the end of surgery. A standard general anaesthetic technique and postoperative analgesia were used. Emetic episodes and safety assessment were performed during the first 24 hours and the next 24 hours after anaesthesia.

Results—The percentage of patients who were emesis free during 0–24 hours after anaesthesia was 85% with granisetron and 90% with ramosetron, respectively (p = 0.369); the corresponding rate during 24–48 hours after anaesthesia was 70% and 95%, respectively (p = 0.003). No clinically serious adverse events caused by the study drug were observed in any of the groups.

Conclusions—Prophylactic antiemetic therapy with ramosetron is comparable to granisetron for the prevention of vomiting during 0–24 hours after anaesthesia in children undergoing strabismus surgery. During 24–48 hours after anaesthesia, ramosetron is more effective than granisetron for prophylaxis against postoperative vomiting.

(Br J Ophthalmol 2001;85:670–672)

Children undergoing strabismus surgery are considered to be at a remarkably high risk for developing postoperative vomiting.¹ Most of the currently used antiemetics (antihistamines, butyrophenones, dopamine receptor antagonists) have been reported to occasionally cause undesirable adverse effects such as excessive sedation, hypotension, dry mouth, dysphoria, hallucinations, and extrapyramidal symptoms.² Granisetron, like ondansetron, is a selective 5-hydroxytryptamine type 3 (5HT₃) receptor antagonist, and is effective for the treatment of emesis in patients receiving cytotoxic drugs.³ Granisetron reduces the incidence of vomiting following strabismus surgery in children.⁴,⁵ Ramosetron, (R)-5-[(1-methyl-3-indolyl)carboxyl]-4,5,6,7-tetrahydro-1H-benzimidazol hydrochloride (Nasea; Yamamouchi, Tokyo, Japan) is another new 5HT₃ receptor antagonist, and has more potent and longer acting properties against cisplatin induced emesis than granisetron. Prophylactic therapy with ramosetron is more effective than granisetron for the prevention of postoperative nausea and vomiting within a 24 hours anaesthetic period in women undergoing major gynaecological surgery.⁶ However, there have been no reports comparing the efficacy of ramosetron and granisetron in children. This prospective, randomised, double blinded study was designed to evaluate the efficacy and safety of granisetron and ramosetron for the prevention of postoperative vomiting in children undergoing strabismus surgery.

Methods

The study was approved by our institutional ethics committee, and informed consent was obtained from the parents of 80 children (American Society of Anesthesiologists physical status I), aged 4–10 years, undergoing strabismus surgery (that is, operative procedure for eye muscles advancement (resection) and/or recession). Patients who had a history of motion sickness, previous postoperative vomiting, gastrointestinal disorders, or had had an antiemetic within 24 hours before surgery were excluded from participation because these patient related factors might contribute to postoperative vomiting.⁷

Patients were randomly assigned to receive intravenously granisetron 40 µg/kg or ramosetron 6 µg/kg (n = 40 of each) at the completion of the surgical procedure. A randomisation list was generated and identical syringes containing each drug were prepared by personnel not involved in the study, according to the list. The dose of granisetron chosen in this study was used in our previous study.⁸ No data were available regarding the dose of ramosetron to be used in paediatric patients, but the dose used in the present study was extrapolated from the adult investigation.⁹

Patients were not allowed to have solid food after midnight before surgery. Clear liquids were permitted up to 3 hours before surgery. No preanaesthetic medications were administered. Anaesthesia was induced by increasing concentration of sevoflurane in 66% nitrous oxide (N₂O) and oxygen (O₂) via mask. After
Values are number (%).

24–48 hours after anaesthesia

Vomiting 9 (23) 2 (5) 0.024 4.60 (1.35–17.73)
Retching 5 (13) 0 (0) 0.027 13.0 (0.90–188.42)
No emesis 28 (70) 38 (95) 0.003 0.74 (0.02–0.88)

Vomiting 6 (15) 4 (10) 0.369 1.50 (0.55–4.06)
Retching 1 (3) 2 (5) 0.5 0.60 (0.09–3.87)
No emesis 34 (85) 36 (90) 0.369 0.94 (0.82–1.09)

Table 1 Patient demographic data

<table>
<thead>
<tr>
<th></th>
<th>Granisetron (n=40)</th>
<th>Ramusetron (n=40)</th>
<th>p Value</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>6.6 (2.2)</td>
<td>6.7 (2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>20/20</td>
<td>18/22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>119.2 (10.4)</td>
<td>119.7 (11.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>23.6 (5.3)</td>
<td>24.1 (7.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>48 (10)</td>
<td>47 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>71 (10)</td>
<td>69 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle repaired (n)</td>
<td>2.2 (0.5)</td>
<td>2.4 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of surgery (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advancement (resection)</td>
<td>2 (3)</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recession</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>Advancement and recession</td>
<td>35</td>
<td>34</td>
<td></td>
<td></td>
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<tr>
<td>Analgesics administered postoperatively (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>29</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentazocine</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD) or number.

Table 2 Number (%) of patients experiencing no emesis, or with retching or vomiting during 0–24 hours and 24–48 hours after anaesthesia

<table>
<thead>
<tr>
<th></th>
<th>Granisetron (n=40)</th>
<th>Ramusetron (n=40)</th>
<th>p Value</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–24 hours after anaesthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No emesis</td>
<td>34 (85)</td>
<td>36 (90)</td>
<td>0.369</td>
<td>0.94 (0.82–1.09)</td>
</tr>
<tr>
<td>Retching</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>0.5</td>
<td>0.60 (0.09–3.87)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (15)</td>
<td>4 (10)</td>
<td>0.369</td>
<td>1.50 (0.55–4.06)</td>
</tr>
<tr>
<td>24–48 hours after anaesthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No emesis</td>
<td>28 (70)</td>
<td>38 (95)</td>
<td>0.003</td>
<td>0.74 (0.02–0.88)</td>
</tr>
<tr>
<td>Retching</td>
<td>5 (13)</td>
<td>0 (0)</td>
<td>0.027</td>
<td>13.0 (0.90–188.42)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (23)</td>
<td>2 (5)</td>
<td>0.024</td>
<td>4.60 (1.35–17.73)</td>
</tr>
</tbody>
</table>

Values are number (%).
used in the present study was used in our previous studies. Therefore, the differences in the number of patients experiencing no emesis between the groups can be attributed to the study drug. An emesis free episode observed in this study would be changed if such patient related factors were not controlled.

Granisetron is effective for the treatment of emesis induced by cancer chemotherapy. We have demonstrated that granisetron reduces the incidence of vomiting after paediatric strabismus surgery, and have also shown that granisetron 40 µg/kg is the minimum effective dose for the prevention of postoperative vomiting. Therefore, the same dose of granisetron was administered in the present study. The precise mechanism for the prevention of postoperative vomiting remains unclear, but it has been suggested that granisetron may act on sites containing 5HT, receptor with demonstrated antiemetic effects. Ramosetron, another 5HT, receptor antagonist, is effective for the treatment of cisplatin induced emesis. Our results demonstrated that ramosetron, like granisetron, reduces the incidence of vomiting after strabismus surgery in children. The exact mechanism of ramosetron for the prevention of postoperative vomiting is unknown, but it may act at the area postrema and the nucleus tractus solitarius, which contain a number of 5HT, receptors. Thus, the possible mechanism of ramosetron for the prevention of postoperative vomiting is similar to that of granisetron. The dose of ramosetron used for children has not been established, but was extrapolated from clinical trials in adults.

In this study, we showed that the number of patients experiencing no vomiting 24–48 hours after anesthesia was greater in those who had received ramosetron than in those who had not (p = 0.003) and also showed no differences in emesis free episodes during 0–24 hours after anaesthesia between the groups (p = 0.369). These findings suggest that ramosetron has a potent antiemetic effect that lasts up to 48 hours. The exact reason for the difference in effectiveness between granisetron and ramosetron is not known, but may be related to the elimination half life (granisetron 3.1 hours versus ramosetron 5.8 hours) and/or the affinities of 5HT, receptor antagonists (granisetron 1 versus ramosetron 41).

Granisetron lacks the sedative, dysphoric, and extrapyramidal symptoms associated with other non-5HT, receptor antagonists such as droperidol and metoclopramide. We have recently demonstrated that granisetron is relatively free of adverse effects and is also safe for the prevention of vomiting following paediatric strabismus surgery. Adverse events caused by the study drug in the present study were not clinically serious in either group. Thus, ramosetron, like granisetron, is considered to be relatively free of adverse effects.

The major deficiency in this study design is the failure to include a control group receiving placebo. We have already shown that the antiemetic efficacy of granisetron is superior to placebo for the prevention of vomiting after strabismus surgery in children. Moreover, Aspinal and Goodman have suggested that placebo control in clinical trials may be of active drugs are available because postoperative nausea and vomiting are common and distressing symptoms against which there is effective treatment. Therefore, a control group was not included in the present study.

In Japan, a 5HT, receptor antagonist, granisetron ($102.00 for 3 mg) or ramosetron ($100.00 for 0.3 mg), is much more expensive than other commonly used and well established antiemetics, droperidol ($1.80 for 1.25 mg) and metoclopramide ($0.60 for 10 mg). However, the use of these non-5-HT3 receptors as antiemetics has been limited because these drugs occasionally cause excessive sedation and/or extrapyramidal symptoms. Therefore, the choice of an antiemetic should not be based solely on the calculation of costs, but also should take into consideration the preference of patient.

In conclusion, prophylactic antiemetic therapy with ramosetron is comparable to granisetron for the prevention of vomiting during 0–24 hours after anaesthesia in children undergoing strabismus surgery. During 24–48 hours after anaesthesia, ramosetron is more effective than granisetron for prophylaxis against postoperative vomiting.

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Notice of formal retraction of article by Dr Y. Fujii. This article is being retracted as a result of:
(1) Overwhelming evidence of fabrication, related to the fact that the distributions of many variables reported by Dr Fujii in these studies could not have occurred by chance;1 2 and
(2) The inability of Dr Fujii’s institutions to attest to the integrity of the study and/or its data conducted under their auspices, as set out in the Joint Editors-in-Chief Request for Determination of April 9, 2012.3

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REFERENCES