

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

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Abstract

Background/claims—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% (p = 0.003). No clinically serious adverse events caused by the study drug were observed in any of the groups.

Conclusion—Prophylactic antiemetic therapy with ramosetron is comparable with 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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emesis in patients receiving cytotoxic drugs.⁴ Granisetron reduces the incidence of vomiting following strabismus surgery in children.⁵ Ramosetron, (R)-5-[(1-methyl-3-indolyl)carboxyl]-4,5,6,7-tetrahydro-1H-benzimidazol hydrochloride (Nasea; Yamanouchi, Tokyo, Japan) is another new 5HT₃ receptor antagonist, and has more potent and longer acting properties against cisplatin induced emesis than granisetron.⁶ Prophylactic therapy with ramosetron is more effective than granisetron for the prevention of postoperative nausea and vomiting within a 48 hour postanaesthetic period in women undergoing major gynaecological surgery.⁷ 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.³

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.⁵ 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.⁷

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

Children undergoing strabismus surgery are considered to be at a remarkably high risk for developing postoperative vomiting.^{1,2} 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.³ Granisetron, like ondansetron, is a selective 5-hydroxytryptamine type 3 (5HT₃) receptor antagonist, and is effective for the treatment of

Table 1 Patient demographic data

	Granisetron (n=40)	Ramosetron (n=40)
Age (years)	6.6 (2.2)	6.7 (2.4)
Sex (male/female)	20/20	18/22
Height (cm)	119.2 (10.4)	119.7 (11.2)
Weight (kg)	23.6 (5.3)	24.1 (7.0)
Duration of surgery (min)	48 (10)	47 (12)
Duration of anaesthesia (min)	71 (10)	69 (11)
Muscle repaired (n)	2.2 (0.5)	2.4 (0.4)
Types of surgery (n)		
Advancement (resection)	2	3
Recession	3	3
Advancement and recession	35	34
Analgesics administered postoperatively (n)		
Acetaminophen	29	30
Pentazocine	5	5

Values are mean (SD) or number.

an inhalation induction of anaesthesia, atropine 0.01 mg/kg was given intravenously and tracheal intubation was facilitated with vecuronium 0.1 mg/kg intravenously. After tracheal intubation, anaesthesia was maintained with N₂O/O₂ (2:1) and sevoflurane 1.0%–3.0% (inspired concentration). Ventilation was mechanically controlled and adjusted to maintain an end tidal carbon dioxide tension at 4.6–5.2 kPa using an anaesthetic/respiratory gas analyser. Neuromuscular block was achieved with vecuronium and was antagonised by a combination of atropine 0.02 mg/kg and neostigmine 0.04 mg/kg intravenously at the end of surgery. The trachea was extubated when the patient was awake. Rectal temperature was monitored and maintained at 37°C (SD 1°C) using hot water pads throughout surgery. After operation, all patients were admitted to the hospital and remained for a couple of days. Clear liquids were offered only if requested by the patient, and other oral intake was not allowed for 4 hours after recovery from anaesthesia. Postoperative analgesia was provided by acetaminophen 15–20 mg/kg rectally for mild pain and by pentazocin 0.3 mg/kg intravenously for severe pain.

After operation, all episodes of emetic symptoms (retching, vomiting) during 0–24 hours and 24–48 hours after anaesthesia were recorded by nursing staff without any knowledge of which treatment each patient had received. These nurses observed the patients at various intervals according to the normal ward routine and asked the parents about their children's postoperative condition (that is, no emesis, vomiting, retching). Vomiting was defined as the forceful expulsion of gastric contents from the mouth, and retching was defined as the laboured, spasmodic, rhythmic contraction of

the respiratory muscles, including the diaphragm, chest wall, and abdominal wall muscles, without the expulsion of gastric contents.³ Nausea was not assessed as a separate entity in this study because of the young age of the patients. The problems (that is, adverse events due to the study drugs) were also recorded after by either questioning the children, interviewing the parents of patients, or observation by the nurses.

Patient data were analysed using ANOVA with Bonferroni's adjustment for multiple comparison and χ^2 test. The number of patients with no emesis, or were retching or vomiting, and the incidence of adverse events were compared with Fisher's exact probability test. A p value of <0.05 was considered significant. Values are expressed as mean (SD) or number (%). Forty patients in each group were sufficient to detect a difference with $\alpha = 0.05$ and power $(1 - \beta) = 0.8$.

Results

Patient profile and information on surgery and anaesthesia are summarised in Table 1. The treatment groups were comparable with regard to patient characteristics and types of operation. The percentage of patients with no emesis during 0–24 hours after anaesthesia was 85% with granisetron and 90% with ramosetron, respectively (p = 0.369, relative risk 0.94 (0.82–1.09)); the corresponding rate during 24–48 hours after anaesthesia was 70% and 95% (p = 0.003, relative risk 0.74 (0.62–0.88)). Thus, an emesis-free episode during 24–48 hours after anaesthesia was greater in patients who had received ramosetron than in those who had received granisetron (p <0.05) (Table 2). Clinically serious adverse events (excessive sedation, extrapyramidal symptoms) caused by the study drug were not observed in any of the groups.

Discussion

The reported incidence of vomiting after paediatric strabismus surgery varies from 48% to 85% when no prophylactic antiemetic is given.^{1,2} This incidence is higher than that associated with other surgical procedures in children.³ The cause of vomiting following paediatric strabismus surgery remains unclear, but is probably multifactorial.³ A number of factors including age, sex, obesity, a history of motion sickness, and/or previous postoperative vomiting, operative procedure, anaesthetic technique, and postoperative pain are considered to affect the incidence of postoperative vomiting.³ Surgical factors also include the impulses from the extrinsic eye muscles related to the vestibular nuclei III, IV, and VI of the medial longitudinal fasciculi.⁸ These vestibular nuclei lie in the brainstem reticular formation and are closely associated anatomically with the vomiting centre. In this study, however, the treatment groups were comparable with respect to patient characteristics, operative procedure, anaesthetics administered, and analgesics used postoperatively. A neuromuscular blocking drug is also an integral part of a balanced anaesthetic technique. The dose (0.1 mg/kg) of vecuronium

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

	Granisetron (n=40)	Ramosetron (n=40)	p Value	Relative risk (95% CI)
0–24 hours after anaesthesia				
No emesis	34 (85)	36 (90)	0.369	0.94 (0.82–1.09)
Retching	1 (3)	2 (5)	0.5	0.60 (0.09–3.87)
Vomiting	6 (15)	4 (10)	0.369	1.50 (0.55–4.06)
24–48 hours after anaesthesia				
No emesis	28 (70)	38 (95)	0.003	0.74 (0.62–0.88)
Retching	5 (13)	0 (0)	0.027	13.0 (0.90–188.42)
Vomiting	9 (23)	2 (5)	0.024	4.60 (1.35–17.73)

Values are number (%).

used in the present study was used in our previous studies.⁵⁻⁷ 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.⁴ We have demonstrated that granisetron reduces the incidence of vomiting after paediatric strabismus surgery,⁵ and have also shown that granisetron 40 µg/kg is the minimum effective dose for the prevention of postoperative vomiting.⁹ 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 5HT₃ receptor with demonstrated antiemetic effects.¹⁰ Ramosetron, another 5HT₃ receptor antagonist, is effective for the treatment of cisplatin induced emesis.¹¹ 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 5HT₃ receptors.¹² Thus, the possible mechanism of ramosetron for the prevention of postoperative vomiting is similar to that of granisetron. The dose of ramosetron to be used for children has not been established, but was extrapolated from clinical trial in adults.⁷

In this study, we showed that the number of patients experiencing no emesis during 24–48 hours after anaesthesia was greater in those who had received ramosetron than in those who had received granisetron ($p = 0.003$), 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)¹³⁻¹⁴ and/or the affinities of 5HT₃ receptor antagonists (granisetron 1 versus ramosetron 41).⁶

Granisetron lacks the sedative, dysphoric, and extrapyramidal symptoms associated with other non-5HT₃ receptor antagonists such as droperidol and metoclopramide.¹⁵ 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.⁵ 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.⁵ Moreover, Aspinall and Goodman¹⁶ have suggested that placebo controlled trials may be unethical if 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 5HT₃ 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.³ Therefore, the choice of antiemetics should not be based solely on the calculation of costs, but also should take into consideration the preference of patients.

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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