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Oral granisetron for strabismus surgery in children

Purpose: To determine the efficacy of oral granisetron in preventing postoperative vomiting (POV) following strabismus repair in children.

Methods: In a randomized, double-blind, placebo-controlled trial, 73 pediatric patients received either placebo, 20 $\mu g \cdot kg^{-1}$ or 40 $\mu g \cdot kg^{-1}$ granisetron *po* 20 min before induction of anesthesia. No premedication was given, induction was with halothane and all children breathed spontaneously via a laryngeal mask airway. Maintenance was with isoflurane without the use of opioids. Ketorolac and acetaminophen were used for analgesia. The number of episodes and the severity of vomiting and retching were recorded for the first 24 hr postoperatively, as was the use of rescue antiemetics.

Results: Granisetron 20 $\mu g \cdot kg^{-1}$ and 40 $\mu g \cdot kg^{-1}$ were more effective than placebo in reducing the incidence of POV during the first 24 hr (29% in both the granisetron groups *vs* 84% in the placebo group, $P < 0.05$). In addition, the number of children experiencing severe vomiting (≥ 3 episodes) was reduced in the granisetron 20 $\mu g \cdot kg^{-1}$ and 40 $\mu g \cdot kg^{-1}$ groups compared with placebo (4%, 8% and 48% respectively, $P < 0.05$). Patients in the granisetron group were discharged home earlier (105 min *vs* 124 min, $P = 0.04$). There was no difference in the incidence of POV between the two granisetron groups.

Conclusion: Preoperative oral granisetron in a dose of 20 $\mu g \cdot kg^{-1}$ provided effective prophylaxis against POV in children undergoing stabismus repair.

Objectif : Déterminer l'efficacité du granisétron, administré par voie orale, à prévenir les vomissements postopératoires (VPO) suivant la correction du strabisme chez des enfants.

Méthode : Lors d'un essai contre placebo, en double aveugle, 73 patients pédiatriques ont reçu soit un placebo, soit 20 $\mu g \cdot kg^{-1}$ ou 40 $\mu g \cdot kg^{-1}$ de granisétron *po* 20 min avant l'induction de l'anesthésie. Aucune prémédication n'a été administrée, l'induction s'est faite avec de l'halothane et l'anesthésie a été maintenue chez tous les enfants en utilisant la ventilation spontanée au moyen d'un masque laryngé. On a maintenu l'anesthésie avec de l'isoflurane sans employer d'opioïdes. Les analgésiques étaient du kétorolac et de l'acétaminophène. Le nombre et la sévérité des épisodes de vomissements et de haut-le-coeur ont été notés, pendant les vingt-quatre premières heures postopératoires, de même que le recours à des antiémétiques.

Résultats : Le granisétron à 20 $\mu g \cdot kg^{-1}$ et à 40 $\mu g \cdot kg^{-1}$ a été plus efficace que le placebo en réduisant l'incidence des VPO pendant les vingt-quatre premières heures (29 % dans les deux groupes qui ont reçu du granisétron *vs* 84 % dans le groupe qui a reçu le placebo, $P < 0,05$). De plus, le nombre d'enfants qui ont eu des vomissements sévères (≥ 3 épisodes) était réduit dans les groupes recevant du granisétron en doses de 20 $\mu g \cdot kg^{-1}$ et de 40 $\mu g \cdot kg^{-1}$ à comparer au groupe recevant le placebo (4 %, 8 % et 48 % respectivement, $P < 0,05$). Les patients du groupe granisétron ont reçu leur congé plus tôt (105 min *vs* 124 min, $P = 0,04$). Il n'y a pas eu de différence entre les deux groupes qui ont reçu du granisétron concernant l'incidence des VPO.

Conclusion : L'administration orale préopératoire de granisétron en doses de 20 $\mu g \cdot kg^{-1}$ prévenait de façon efficace les VPO chez les enfants ayant subi une correction de strabisme.

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POSTOPERATIVE nausea and vomiting (PONV) is common after strabismus repair in children,[1] and may lead to delayed discharge or unanticipated hospital admission. The 5-hydroxytryptamine subtype 3 (5-HT_3) antagonists ondansetron and granisetron have been shown to be effective against both chemotherapy-induced and postoperative vomiting in children[2–5] but are expensive when used intravenously. Rose *et al.* recently showed that preoperative oral ondansetron administered prior to tonsillectomy was associated with reduced postoperative vomiting (POV) in pre-adolescent children and resulted in cost savings when compared with the use of the *iv* preparation.[6] To date, there are no data on the effective dose of an oral preparation of granisetron, and since it can be compounded from tablet form with a long shelf-life,[7] its use could reduce the cost and wastage when compared with the *iv* preparation. In this randomized, double-blind, placebo controlled trial, we compared two doses of oral granisetron, 20 $\mu g \cdot kg^{-1}$ and 40 $\mu g \cdot kg^{-1}$ with placebo for the prophylaxis of POV following strabismus repair in children.

Methods

Following Institutional Review Board approval and written consent from the parents, 76 children ASA physical status 1-2, aged 1-12 yr (mean 5.1 yr) scheduled for strabismus correction on an outpatient basis, were enrolled. Exclusion criteria included a known allergy to 5-HT_3 antagonists or recent use of a drug with a known antiemetic effect. All patients were fasted for at least four hours for clear liquids and for six hours for solids. No preoperative sedation was administered. Patients were randomly assigned using computer-generated random numbers to one of three groups. Twenty minutes before induction of anesthesia, all patients received in a double-blind fashion, placebo, 20 $\mu g \cdot kg^{-1}$ or 40 $\mu g \cdot kg^{-1}$ granisetron. Acceptance of the formulation was scored as follows: 1 = accepted readily, 2 = accepted reluctantly, 3 = restrained, 4 = refused or spat out.

The suspension was prepared in advance by the hospital pharmacy using 1 mg granisetron tablets suspended in Ora-Plus™ (Paddock Labs, Inc, Minneapolis, MN) with strawberry syrup to achieve a concentration of 400 $\mu g \cdot ml^{-1}$ whereas the placebo was strawberry syrup without the granisetron. The oral formulation was drawn up in syringes and all patients received a standard volume of 0.1 $ml \cdot kg^{-1}$ with both the anesthesiologist and nurse blinded to its contents.

Anesthesia was induced with halothane and nitrous oxide 66% in oxygen *via* face mask. Intravenous access was obtained and a laryngeal mask airway (LMA) was inserted under deep inhalation anesthesia. All patients received 0.5 $mg \cdot kg^{-1}$ ketorolac *iv*, 10 $\mu g \cdot kg^{-1}$ glycopyrrolate *iv*, and 20 $mg \cdot kg^{-1}$ acetaminophen *pr*. Anesthesia was maintained with nitrous oxide and isoflurane and intravenous fluids were administered as per existing protocols to replace preoperative deficits and to provide standard maintenance requirements. At the completion of surgery, the LMA was removed and an oro-gastric tube was inserted to suction the stomach.

Pain was assessed according to a 10 point objective scale (1 = no pain, 10 = worst pain) and, at the discretion of the post anesthesia care unit (PACU) nurse, was treated with 0.05 $mg \cdot kg^{-1}$ morphine *iv* (typically for a score ≥ 5). The time from the end of surgery to first response to commands, first oral intake and discharge readiness were recorded, as well as any episodes of nausea, vomiting and retching. Vomiting was defined as the forceful expulsion of gastric contents, retching was rhythmic contraction of the diaphragm without expulsion of gastric contents. Both were considered as emetic episodes. The severity of emesis was defined as mild (1 episode), moderate (2 episodes) and severe (≥ 3 episodes). Children with more than one episode of vomiting or retching were given 0.15 $mg \cdot kg^{-1}$ metoclopramide *iv*.

The patients were discharged when our standard criteria were met, which includes stable vital signs and minimal pain or emesis. Tolerance of oral fluids was not required before discharge. Twenty-four hours postoperatively, a follow-up telephone call was made to determine the incidence and severity of emesis on the trip home and during the initial 24 hr, as well as the use of antiemetic and analgesics and the incidence of side effects associated with 5-HT_3 antagonists (headache and abdominal pain).

Statistical Methods

A power analysis performed before the study required 24 patients per group in order to detect a reduction in the incidence of 24 hr emesis of 50%, assuming an incidence of 70% in the placebo group ($\alpha = 0.05$; $ß = 0.20$). Continuous data were analyzed by one-way ANOVA and nominal data were compared by chi-square and Fisher's exact test where appropriate. All tests were two-sided, significance was defined as $P < 0.05$.

Results

Seventy-six children were enrolled, but three refused or spat out the study medication and were excluded from further analysis. There were no differences among the three groups with respect to age, weight, gender, ASA physical status, number of eye muscles operated on, or duration of anesthesia and surgery (Table I). Sixty-two children (85%) readily accepted

TABLE I Demographic and Intraoperative Data [mean ± SD, or mode (range)]

Group	*Placebo* (*n* = 25)	*Granisetron 20 μg·kg⁻¹* (*n* = 24)	*Granisetron 40 μg·kg⁻¹* (*n* = 24)
Age (yr)	5.6 ± 2.9	4.5 ± 2.3	4.9 ± 3.3
Weight (kg)	22.2 ± 7.7	21.7 ± 11.3	20.3 ± 9.4
Gender (M/F)	13 / 12	9 / 15	12 / 12
Number of muscles	2 (1-4)	2 (1-4)	2 (1-4)
Duration of surgery (min)	41.9 ± 16.4	47.7 ± 17.2	45.6 ± 18.8
Duration of anesthesia (min)	68.8 ±17.6	68.2 ± 12.7	72.0 ± 22.2

TABLE II Postoperative Data [mean ± SD, or n]

Group	*Placebo* (*n* = 25)	*Granisetron 20 μg·kg⁻¹* (*n* = 24)	*Granisetron 40 μg·kg⁻¹* (*n* = 24)
Time to awakening (min)	25.0 ± 17.0	31.0 ± 20.0	21.0 ± 17.0
Time to oral fluids (min)	74.0 ± 33.0	62.0 ± 25.0	61.0 ± 27.0
Antiemetics administered	9	1*	4
Opioids administered	9	9	8
Time to discharge readiness	124.0 ± 34.6	104.8 ± 33.9*	104.7 ± 36.3*
Headache	8	3	3
Abdominal pain	0	1	3

* $P < 0.05$ compared with placebo

the study medication, 10 (14%) were reluctant to take it and one child required restraint. There were no differences among groups in time to first response, total *iv* fluids administered, analgesic requirements or in the incidence of headache or abdominal pain (Table II).

The incidence of in-hospital vomiting was 6/24 (25%) in the granisetron 20 μg·kg⁻¹ group, 5/24 (21%) in the granisetron 40 μg·kg⁻¹ group 13/25 (52%) in the placebo group ($P < 0.05$). The incidence of vomiting in the first 24 hr was 7/24 (29%) in both the granisetron 20 μg·kg⁻¹ and 40 μg·kg⁻¹ groups, compared with 21/25 (84%) in the placebo group ($P < 0.05$). In addition, the number of children experiencing severe vomiting (≥ 3 episodes) was less in the granisetron 20 μg·kg⁻¹ and 40 μg·kg⁻¹ groups than in the placebo group (1/24, 2/24 and 12/25 respectively, $P < 0.05$). Patients in the granisetron groups required fewer rescue antiemetics and were ready for discharge from the PACU earlier (105 ± 34.3 min *vs* 124 ± 34.6 min, $P = 0.04$). There were no differences in the incidence and severity of POV between

TABLE III Incidence and Severity of Postoperative Vomiting in the first 24 hr [n]

Group	*Placebo* (*n* = 25)	*Granisetron 20 μg·kg⁻¹* (*n* = 24)	*Granisetron 40 μg·kg⁻¹* (*n* = 24)
incidence of emesis			
in-hospital	13	6 *	5 *
journey home	14	1 *	1 *
home emesis	12	1 *	3 *
24 hr emesis	21	7 *	7 *
severity of emesis			
none (0 episodes)	4	17 *	17 *
mild (1 episode)	7	6	3
moderate (2 episodes)	2	0	2
severe (3 episodes)	12	1 *	2 *

* $P < 0.05$ compared with placebo

the 20 μg·kg⁻¹ and 40 μg·kg⁻¹ granisetron dose. No children were admitted to hospital due to prolonged POV.

Discussion

This study showed that preoperative oral granisetron reduced both the incidence and severity of POV compared with placebo in the first 24 hr following outpatient strabismus surgery in children. However, it should be noted that, despite the equal efficacy of both doses of granisetron in reducing the incidence of POV compared with placebo, we were unable to detect any further differences in the incidence between individual doses. Although this may be a true observation, the possibility of a type II error should not be ignored.

The doses of 20 μg·kg⁻¹ and 40 μg·kg⁻¹ were chosen based upon previously published papers. Fujii *et al.* demonstrated that 40 μg·kg⁻¹ granisetron *iv* was the optimal dose for preventing emesis following strabismus repair and tonsillectomy.[8] The same authors showed that 40 μg·kg⁻¹ granisetron *iv* was more effective than placebo, metoclopramide and droperidol in reducing the incidence of POV after pediatric surgery.[5] In addition, Cieslak *et al.* showed that a dose of 10 μg·kg⁻¹ *iv* was ineffective in the prophylaxis of pediatric PONV, whereas 40 μg·kg⁻¹ *iv* reduced the incidence of PONV from 42% in the control group to 9%.[4] In this study we chose a lower 20 μg·kg⁻¹ dose as it was cheaper.

The antiemetic action of the 5-HT_3 antagonists is thought to be mediated by blocking the action of serotonin at receptor sites both centrally within the chemoreceptor trigger zone (CTZ) and the nucleus tractus solitarius, and peripherally on the vagal afferents from the gastrointestinal tract. Granisetron is a more selective

5-HT_3 receptor antagonist than ondansetron with a longer duration of action.[9] Our results showed a high incidence of POV in the placebo group (84%) which is comparable to other studies of strabismus surgery where a prophylactic antiemetic was not used.[10] Many factors contribute to PONV following strabismus surgery, including the use of opioids,[11] propofol,[12] nitrous oxide[13] and various antiemetics,[14] and this makes direct comparison of our results with other studies difficult. However, Shendel *et al.* showed that 150 $\mu g \cdot kg^{-1}$ ondansetron *iv* reduced the incidence of PONV during the first 24 postoperative hr to over half that of the placebo group (34.5% *vs* 71.7%), whereas metoclopramide had no effect.[10] In our study, early or pre-discharge emesis was reduced by approximately 50% by the use of granisetron. However, of note was the extremely low incidence of emesis after discharge from hospital which supports the long duration of action of 5-HT_3 antagonists that has been demonstrated with ondansetron.[10] The need for rescue antiemetics was lower in the treatment groups and time to discharge readiness was nearly 20 min earlier in the granisetron groups ($P < 0.05$) which may have economic implications. The side effects known to be associated with 5-HT_3 receptor antagonists include headache and abdominal pain. There was no difference among groups regarding these side effects.

Granisetron has been associated with high costs. However, the use of tablets to prepare an oral formulation suitable for children resulted in reduced costs with ondansetron.[6] The flavoured syrup was prepared using 1 mg tablets to achieve a concentration of 400 $\mu g \cdot ml^{-1}$ as described by Quercia *et al.*[7] This extemporaneously prepared formulation is stable for up to 30 days at temperatures between 5 and 24°C and can therefore be used for multiple dosing with little wastage. The 1 mg tablet costs US$31.17 compared with $92.02 for 1 mg of the *iv* preparation. This contrasts with ondansetron which is available in a commercially prepared oral syrup (4 $mg \cdot 5ml^{-1}$) at $\$2.22 \cdot ml^{-1}$. If one assumes that granisetron and ondansetron have similar outcomes, then a dose of oral ondansetron 150 $\mu g \cdot kg^{-1}$ is comparable in price ($\$0.42 \cdot kg^{-1}$ *vs* $\$0.63 \cdot kg^{-1}$). This is in sharp contrast to metoclopramide and droperidol which each cost less that $0.80 per multidose vial.

In conclusion, this study showed that 20 $\mu g \cdot kg^{-1}$ granisetron *po* administered 20 min before surgery was effective in reducing the incidence and severity of POV following strabismus repair in children, resulting in earlier time to discharge from hospital. Despite this, the relatively high cost of granisetron needs to be considered when choosing this antiemetic and balanced against potential benefits in terms of patient comfort and reduced hospital stay.

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