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Prophylactic Ondansetron in Prevention of Postoperative Nausea and Vomiting following Pediatric Strabismus Surgery

A Dose-Response Study

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Background: **This study evaluated the antiemetic effectiveness, dose–response, and clinical usefulness of prophylactic ondansetron in the prevention of postoperative nausea and vomiting (PONV) in children undergoing strabismus repair.**

Method: **The authors observed 180 children, American Society of Anesthesiologists physical status I or II, 2–12 yr of age, who were undergoing strabismus repair. After induction of anesthesia with halothane and nitrous oxide in oxygen or intravenous thiopental, children received either placebo (saline) or intravenous ondansetron in doses of 25, 50, 75, 100, and 150 μg/kg (n = 30). The trachea was intubated and ventilation was controlled. Perioperative analgesic and fluid requirements were standardized. Episodes of nausea and vomiting were recorded for the first 24 h postoperatively. Data such as nonsurrogate (parental satisfaction scores and duration of postanesthesia care unit stay) and therapeutic (numbers needed to prevent and harm) outcome measures were collected.**

Results: **The incidences of PONV in the placebo and 25-, 50-, 75-, 100-, and 150-μg/kg ondansetron groups were 83, 77, 47, 30, 30, and 27%, respectively. The incidence was less in the 75- ($P = 0.002$), 100- ($P = 0.002$), and 150-μg/kg ($P < 0.001$) ondansetron groups compared with placebo. Duration of stay in the postanesthesia care unit was shorter in the 75-, 100-, and 150-μg/kg ondansetron groups ($P < 0.002$) compared with the placebo group. Parental assessment scores for the child's perioperative experience and the positive number needed to prevent PONV were also better and favorable in the 75-, 100-, and 150-μg/kg ondansetron groups compared with the placebo group. The incidence ($P > 0.99$) and severity ($P = 0.63$) of PONV were similar in the 75- and 150-μg/kg ondansetron groups. Surrogate, nonsurrogate, and therapeutic outcome measures revealed that 75 μg/kg ondansetron provided the same benefits as did 100 and 150 μg/kg.**

Conclusion: **The routine prophylactic use of ondansetron at a dose of 75 μg/kg is as effective as 150 μg/kg in preventing PONV and improving the "true" outcome measures after strabismus repair in children. (Key words: Emesis; PONV.)**

POSTOPERATIVE nausea and vomiting (PONV) remains a distressing and common problem after strabismus repair, despite the use of available antiemetics. Ondansetron is commonly used because of its effectiveness and safety compared with alternative antiemetics, but its use has been criticized because most studies that evaluated the effects of ondansetron on PONV reported surrogate outcome measures, such as incidence of PONV or number of emetic episodes per patient, rather than more meaningful outcome measures, such as patient satisfaction, duration of hospital stay, and incidence of unanticipated hospital admission.[1] A recent meta-analysis, which reviewed the effectiveness and safety data for ondansetron for preventing PONV, has challenged routine prophylactic use of ondansetron based on benefit and risk data and stated that effectiveness of ondansetron in children has been poorly documented.[2] No clinical trial has evaluated the dose effectiveness and clinical usefulness of prophylactic ondansetron in a homogenous pediatric population undergoing strabismus repair with more important "true" outcome measures, such as patient comfort (parental assessment scores), and measures that help in therapeutic decision-making to assess

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the clinical usefulness of a drug or a practice such as the number needed to treat to prevent one episode of PONV (NNTP) and the number needed to treat to harm (to cause one adverse event) (NNTH). In this study, we aimed to evaluate the effectiveness and the clinical usefulness of "routine" prophylactic ondansetron with clinically more useful nonsurrogate and therapeutic outcome measures in a dose–response fashion in children undergoing strabismus repair.

Materials and Methods

After obtaining institutional review board approval and informed parental consent, in this prospective, randomized, placebo-controlled, double-blind study we enrolled 180 children classified as American Society of Anesthesiologists physical status I or II between the ages of 2 and 12 yr undergoing strabismus repair during general anesthesia. We excluded children who were administered drugs known to have antiemetic effects (*e.g.*, phenothiazines, benzamides, scopolamine, corticosteroids, tricyclic antidepressants) in the 24 h before surgery. Children did not consume milk or solid food for at least 6 h before operation; clear fluids were allowed until 3 h before induction. Children were not premedicated. Anesthesia was induced with halothane and nitrous oxide in oxygen *via* a face mask or with intravenous thiopental. After induction of anesthesia and establishment of venous access, tracheal intubation was facilitated with 100 μg/kg intravenous vecuronium, and anesthesia was maintained with halothane and nitrous oxide, along with 0.75 mg/kg intravenous meperidine. A random-number generator was used to assign each child prospectively to receive either saline placebo or ondansetron in a dose of 25, 50, 75, 100, or 150 μg/kg. All study drugs were prepared in fixed volumes of 5 ml by an anesthetist not otherwise involved in patient care, to maintain the double-blind nature of the study. Intraoperative intravenous fluid management consisted of administration of lactated Ringer's solution sufficient to correct half the preoperative fluid deficit in the first hour, followed by maintenance fluids according to body weight.[3] At the end of the procedure, residual neuromuscular blockade was antagonized with 50 μg/kg neostigmine and 10 μg/kg glycopyrrolate, the stomach was suctioned, and the trachea was extubated while the child was awake.

Postoperatively, all children were transported to the postanesthesia care unit (PACU). The anesthesiologist who provided intraoperative care assessed postanesthetic recovery using the scoring system of Aldrete and Kroulik.[4] Time to achieve complete recovery (score of 10) was recorded for all children. Postoperatively, analgesia was provided if older children reported pain or if younger children cried. Oral ibuprofen 10 mg/kg was given as the analgesic of first choice, and, for pain in children who had PONV in the immediate postoperative period in the PACU, 0.5 mg/kg meperidine was administered intravenously as the analgesic of second choice by the anesthesiologist who provided intraoperative care. Intravenous fluid comprised lactated Ringer's solution, replacing the rest of the fluid deficit and maintenance fluids in the recovery room.

All episodes of PONV in the first 24 h of the postoperative period in the hospital at the intervals of 0–2 h, 2–6 h, and 6–24 h were evaluated using a numeric scoring system for PONV (0 = no nausea or vomiting, 1 = nausea but no vomiting, 2 = vomiting once in 30 min, 3 = two or more episodes of vomiting in 30 min) by the PACU and ward nursing staffs, who were aware of the nature of the study but blind to the study drug and dose. We did not assess nausea in very young children (younger than 6 yr). Any child having a score of 3 was considered to have severe vomiting and was treated with 150 μg/kg intravenous metoclopramide as a rescue antiemetic. If metoclopramide failed to control emesis, 0.5 mg/kg promethazine was used as the rescue antiemetic of second choice.

The criteria for discharge from the PACU to the ward included maintenance of patent airway without assistance, stable vital signs, adequate pain control, and no nausea and vomiting in the first 2 h after surgery. Those children who had PONV in first 2 h of stay were observed in the PACU until they remained PONV free for 1 h.

Finally, at 24 h after surgery, the primary caretaker was asked to give a global assessment of the entire postoperative experience of the child (parental satisfaction score) using an 11-point verbal numeric scoring system (0 = not at all satisfied, 10 = fully satisfied).

Statistical Analysis

Prestudy power analysis determined that 31 and 22 patients would be necessary in each group to have a 90% chance ($\beta = 0.1$) of detecting 40 and 50% relative reductions in PONV, respectively, from our institute basal incidence of 80%, at the 95% confidence interval limits ($\alpha = 0.05$). (The analysis used version 6.0 of Epi Info [Center for Disease Control, and World Health Organization, Switzerland]). This sample size was only based on comparison with the placebo group; intergroup compar-

Table 1. Demographic and Clinical Data

Demographic and Clinical Data	Placebo Group (n = 30)	Ondansetron Groups* (μg/kg)				
		25	50	75	100	150
Age (yr)	6.8 ± 2.8	7.6 ± 2.9	6.6 ± 3.1	6.1 ± 3.4	6.2 ± 3.4	6.0 ± 3.3
Sex (M/F)	15/15	15/15	15/15	13/17	13/17	14/16
Weight (kg)	19.4 ± 8.0	20.5 ± 8.7	19.5 ± 7.6	19.3 ± 10.0	20.6 ± 10.2	18.8 ± 8.9
ASA status I/II	28/2	28/2	28/2	30/0	30/0	29/1
Durations of						
Anesthesia (min)	65.8 ± 16.6	68.4 ± 17.3	67.4 ± 18.1	66.2 ± 18.2	68.4 ± 13.4	65.3 ± 15.8
Surgery (min)	50.0 ± 16.7	52.4 ± 17.4	53.0 ± 17.4	51.0 ± 17.0	53.4 ± 12.0	50.3 ± 15.5
No. of muscles						
1	6/30	7/30	6/30	3/30	3/30	5/30
2	20/30	20/30	19/30	21/30	19/30	22/30
3	2/30	1/30	3/30	2/30	4/30	1/30
4	2/30	2/30	2/30	4/30	4/30	2/30
Recovery time (min)	20.7 ± 16.7	18.3 ± 15.3	21.7 ± 11.3	19.4 ± 10.1	17.2 ± 9.4	19.3 ± 18.7
Requirements of						
Intravenous fluids (ml/kg)	17.1 ± 5.5	18.8 ± 5.9	16.8 ± 5.7	16.4 ± 6.7	16.1 ± 6.6	16.4 ± 5.9
Analgesics (mg/kg)						
Meperidine (IV)						
Intraoperative	15.6 ± 6.8	16.8 ± 8.2	15.6 ± 6.5	15.7 ± 8.3	15.1 ± 6.6	15.2 ± 7.2
Postoperative	7/30	6/30	4/30	2/30	3/30	2/30
Ibuprofen (oral)						
Postoperative	13/30	18/30	16/30	14/30	17/30	18/30

Age, weight, anesthetic, surgical and recovery times, requirements of intravenous fluids and intraoperative meperidine were presented as the mean ± SD. ASA physical status, sex ratio, number of muscles operated on and requirements of postoperative analgesics were presented as the number of children. The demographic and clinical data were comparable in all the groups.

*n = 30 in each group.

ASA = American Society of Anesthesiologists.

isons to detect differences between ondansetron groups with different doses were not feasible with this small sample size. Two sample *t* tests and Mann-Whitney tests were used to compare the ages and weights; durations of surgery, anesthesia, recovery, and PACU stay; perioperative fluid and analgesic requirements; and parental assessment scores of the children's perioperative experiences. The incidence and severity of PONV from 0-6 and 0-24 h, the duration of PACU stay, and the parental satisfaction score were compared for each group with every other group (all 15 pairwise comparisons possible), and the Bonferroni correction for the multiple comparisons was applied for the overall risk of committing a type I error less than 5% ($\alpha = 0.05$). We stratified the incidence of PONV to the anesthetic induction with halothane and thiopental in each group by chi-square analysis and the Fisher exact tests with Yates corrections. Severity of PONV between the ondansetron 75, 100, and 150 μg/kg groups and the placebo group was compared by chi-square analysis and the Fisher exact test with a Yates continuity correction wherever appropriate. The positive NNTP and NNTH (which indicate how many children had to be exposed to ondansetron to prevent one episode of PONV in a child who would have had it, and to cause extra harm in one who would have not had an adverse event had he or she received placebo, respectively) were calculated as the reciprocals of absolute risk reductions of incidences of PONV and headache, respectively, for children who received ondansetron at different doses. Overall P values < 0.05 ($P < 0.003$, corrected for multiple comparisons) were considered to be statistically significant, and data are presented as the mean ± SD unless otherwise specified.

Results

The demographic and clinical data, such as patient age, gender, weight, physical status, duration of surgery and anesthesia, perioperative fluid and analgesic requirements, recovery time, and the number of muscles operated on were similar among all groups (table 1).

The 24-h incidence of PONV (0-24 h) was similar between the placebo and 25-μg/kg ($P > 0.99$) and 50-μg/kg ($P = 0.01$) ondansetron groups; a reduction in the incidence was observed in the 75- ($P = 0.0001$), 100-

Table 2. Incidence and Severity of PONV

PONV Outcome Measures	Placebo Group (n = 30)	Ondansetron Groups* (μg/kg)				
		25	50	75	100	150
PONV incidence (%)						
0–2 h	46.7	46.7	26.7	13.3	13.3	6.7
2–6 h	66.7	50.0	33.3	23.3	16.7	23.3
6–24 h	36.7	40.0	16.3	6.7	3.3	3.3
0–6 h	73.3	63.3	43.3	23.3	16.7	23.3
0–24 h	83.3	76.7	46.7	30.0	30.0	23.3
Incidence of PONV and induction technique						
Halothane	20/24	16/23	3/6	3/6	2/6	1/7
Thiopental	5/6	7/7	11/24	6/24	7/24	6/23
PONV severity						
Children with PONV score of 3	15/30	14/30	4/30	4/30	2/30	4/30
Emetic episodes per child	1.8 ±1.5	1.6 ± 1.5	0.6 ± 1.0	0.5 ± 0.9	0.3 ± 0.6	0.4 ± 0.7

Incidence of PONV at various intervals has been presented as the percentage of children with PONV. Rescue antiemetic requirement and PONV incidence with different induction techniques has been reported as the number of children. The number of emetic episodes per child (EEC) is presented as mean ± SD. The 24-h PONV incidence was less in the 75- ($P = 0.002$), 100- ($P = 0.002$) and 150-μg/kg ($P < 0.001$) groups compared with the placebo group. The incidence of PONV in the early postoperative period (0–6 h) was reduced by ondansetron 75–150 μg/kg compared with the placebo ($P < 0.001$). Even though the requirements of metoclopramide and the EEC were less in ondansetron 50- to 150-μg/kg groups ($0.003 < P < 0.01$) compared with the placebo group, they did not attain statistical significance after the corrections for multiple pair-wise comparisons (overall α risk was 0.05). The incidence ($P > 0.99$) and the severity ($P = 0.63$) of PONV were similar in the ondansetron 75-, 100- and 150-μg/kg groups.

* n = 30 in each group.

PONV = postoperative nausea and vomiting.

($P = 0.0001$), and 150-μg/kg ($P < 0.0001$) groups compared with placebo (table 2). The incidence of PONV in the early postoperative period at the 0–2 and 2–6 h epochs was reduced by ondansetron at 75-, 100-, and 150-μg/kg doses ($P < 0.001$; table 2). The incidences of PONV in children in whom anesthesia was induced with halothane and thiopental in each group were comparable (table 2).

The decreases in the requirements of metoclopramide as a rescue antiemetic and the number of emetic episodes per child were not statistically significant in the 50-, 75-, 100-, and 150-μg/kg ondansetron groups compared with the placebo group ($0.003 < P < 0.01$; table 2). The numbers of children who required promethazine as the rescue antiemetic were 6, 4, 4, 2, 1, and 0 in the placebo and 25-, 50-, 75-, 100-, and 150-μg/kg ondansetron groups, respectively ($P > 0.05$). The incidence ($P > 0.99$; table 2) and the severity ($P = 0.63$) of PONV were similar in the ondansetron 75-, 100-, and 150-μg/kg groups (table 2).

The positive NNTPs were 15, 3, 2, 2, and 2, respectively, in those children who received ondansetron in doses of 25, 50, 75, 100, and 150 μg/kg (table 3). The NNTHs for headache in the 75- and 100-μg/kg ondansetron groups reached infinity, indicating no extra harm because of ondansetron compared with placebo. In the 150-μg/kg ondansetron group NNTH was 30; ondansetron caused headache in 1 in every 30 children exposed, compared with those who received placebo (table 3).

The duration of PACU stay was significantly shorter in the 75- ($P = 0.002$), 100- ($P = 0.001$), and 150-μg/kg ($P < 0.001$) ondansetron groups, compared with the placebo group (table 3).

The parental assessment scores of the children's perioperative experiences were better for those children who received ondansetron in doses of 75 μg/kg or more compared with the placebo group ($P < 0.002$; table 3). Parents of the children who remained free of PONV had statistically significant, higher satisfaction, compared with those of children with PONV in each group (table 3).

Discussion

In children, strabismus repair is associated with the highest incidence of PONV[5], ranging from 41 to 88% in those who did not receive antiemetic prophylaxis.[6,7] The incidence in this study was 83% in children who received placebo (table 3) and is in accordance with previous studies in this population.[5,7] The placebo group was included in this study to eliminate the influence of observer bias on the results and to calculate the more meaningful therapeutic outcome measures: NNTP and NNTH (to calculate the absolute risk reductions).

Table 3. Therapeutic and Nonsurrogate Outcome Measures

PONV Outcome Measures	Placebo Group (n = 30)	Ondansetron Groups* (μg/kg)				
		25	50	75	100	150
No. needed to prevent (NNTP)	—	14.99	2.72	1.87	1.87	1.66
No. needed to harm (NNTH) for headache	—	∞	∞	∞	∞	30
Side effects						
Headache	2	2	1	2	2	3
Constipation	0	0	0	0	0	0
Drowsiness	1	0	0	0	0	0
Duration of PACU stay (min)	154.3 ± 43.1	157.5 ± 36.5	139.5 ± 16.5	127.5 ± 12.7	126.3 ± 12.8	128.3 ± 11
Parental assessment scores of child's comfort	6.3 ± 2.1	6.4 ± 2.7	7.6 ± 2.1	8.1 ± 1.5	8.1 ± 1.4	7.9 ± 1.4
Parental satisfaction scores for children						
With PONV	5.8 ± 1.9	5.7 ± 2.3	6.2 ± 2.2	6.7 ± 1.2	6.8 ± 1.6	6.5 ± 0.9
Without PONV	8.6 ± 0.9	8.9 ± 0.9	8.9 ± 0.8	8.7 ± 0.9	8.7 ± 0.9	8.4 ± 1.3

NNTP, NNTH, and the incidence of side effects are presented as the number of children. Duration of PACU stay and parental satisfaction scores are presented as mean ± SD. The duration of PACU stay was shorter in ondansetron 75- ($P = 0.002$), 100- ($P = 0.001$) and 150-μg/kg ($P < 0.001$) groups compared with the placebo group. Parents of children who received ondansetron at doses ≥75 μg/kg had a higher satisfaction compared with the placebo ($P < 0.002$). The parents of children who remained free of PONV had a higher satisfaction compared to those of children with PONV in the placebo and in all ondansetron groups ($P < 0.01$).

*n = 30 in each group.

PACU = postanesthesia care unit; PONV = postoperative nausea and vomiting.

A previous dose-response study with ondansetron had shown that 50 μg/kg reduces the incidence of PONV after outpatient surgery in a heterogeneous pediatric population.[8] In that trial, the effectiveness of 75 μg/kg ondansetron was not studied, and the incidence of PONV in the placebo group was lower (58%) than in our trial, probably because of inclusion of children undergoing various surgical procedures with a lesser risk of PONV. No study evaluated the dose-response and clinical usefulness of prophylactic ondansetron in a group of children undergoing strabismus repair alone, which carries the highest risk of PONV,[5] with clinically and therapeutically more important true outcome measures.

The cause of PONV after strabismus surgery is complex and depends on several factors, such as patient characteristics, types of surgery, anesthetic technique, and postoperative pain and perioperative fluid therapy. The use of mivacurium, which was not available to us, instead of vecuronium might have reduced the PONV in this study, by allowing a spontaneous recovery from the neuromuscular block or reversal with edrophonium.[9] However, a recent study reported that the incidence of PONV and the need for antiemetics do not increase with the use of neostigmine and glycopyrrolate for reversal of residual muscle paralysis after mivacurium and rocuronium.[10] Moreover, in a systemic review, Tramer and Fuchs-Buder[11] reported that omitting antagonism of neuromuscular block has a non-negligent risk of residual paralysis, even with short-acting neuromuscular blocking agents (NNTH = 30). In the current study, the groups were comparable with respect to patient characteristics, surgical procedure, anesthetics administered, and analgesics and intravenous fluids used in the perioperative period. Therefore, the differences in the incidence and severity of PONV among the groups in this trial can be attributed to the difference in the doses of ondansetron administered.

Ondansetron had been shown to be effective in the prevention of PONV after strabismus repair.[8,12] However, a recent meta-analysis challenged the clinical usefulness of prophylactic ondansetron in preventing PONV based on effectiveness and safety.[2] Although this meta-analysis states that the effectiveness of ondansetron has been poorly documented in children,[2] the validity of meta-analyses as such is limited because they magnify the problems of individual studies.[13] Moreover, meta-analyses might experience "publication bias," nonuniformity of collected data and dependence on published studies that might have used surrogate outcome measures that make their inclusion in a meta-analysis inappropriate.[1] A recent editorial justified the cautious attitude in accepting clinical practice guidelines of therapies for PONV based only on meta-analytic techniques; it concluded that large randomized controlled trials remain the gold standard for determining the best choice among different therapeutic options.[13] Absence of convincing true outcome data, such as patient satisfaction, duration of PACU stay, or unplanned hospital admis-

sions, made the clinical use of routine ondansetron prophylaxis questionable. In our study, we used parental assessment scores of the child's perioperative experience and duration of PACU stay as nonsurrogate outcome measures, and they were found to be significantly better in children who received 75 μg/kg or more ondansetron compared with those receiving placebo (table 3). The surrogate outcome measures of the severity of PONV, the requirement of rescue antiemetics, and the number of emetic episodes per child did not statistically accord well with the true (nonsurrogate) outcome measures, probably because of a larger number of study groups (more corrections for multiple comparisons) and a relatively smaller number of patients in each group.

Tramer *et al.*[2] described that if the risk of PONV is very high (40–80%), 20% of patients receiving an optimal prophylactic dose of ondansetron will not have PONV who would have had PONV had they received placebo. This was calculated using the NNTP.[2,14,15] The NNTP indicates how many children had to be exposed to ondansetron to prevent PONV in one who would have vomited had he or she received placebo. The NNTP has an advantage over the relative risk reduction and odds ratio in that it expresses effectiveness in a manner that incorporates baseline risk without prophylaxis and risk reduction with prophylaxis. Furthermore, it informs clinicians and patients in more concrete terms how much effort they must expend or money they must spend to prevent one event. The NNTP is becoming widely used as a tool for therapeutic decision-making[14] because it facilitates interpretation in terms of patients treated, rather than the less-intuitive probabilities, and conveys statistical and clinical significance to the physician.[14] Although NNTP has therapeutically useful properties, its shortcomings resulting from the data used and its properties must be acknowledged. It does not reflect the fate of other patients who were not benefited by a treatment or the severity of illness. In addition, more or less, the same NNTPs are obtained, with a high baseline risk and a low relative risk reduction as with a low baseline risk and a high relative risk reduction. Tramer *et al.*[2] in their meta-analysis reported that the best NNTP with the best-documented regimens was between 5 and 6. In our trial, NNTP with 75-, 100-, and 150-μg/kg doses of ondansetron was 2 (table 3), which is far superior to the best NNTP of 5 to 6 from the meta-analysis of Tramer *et al.*[2] Although a meta-analysis can provide an overall estimate of therapeutic effectiveness, it may obscure differences between trials. For example, ondansetron had been shown to be effective in preventing PONV after strabismus repair[8,11,12]; but this benefit is obscured or at least diluted if combined in a meta-analysis[2] with the effectiveness of ondansetron in preventing PONV after craniotomy in children in whom it has not been successful,[16] or analyzed with the effectiveness of ondansetron in less than the optimal dose.[8] Analysis using NNTP preferably should be confined to a single, larger trial to have uniformity in all data, and to specific patient characteristics and surgical procedures; otherwise it results in misinterpretation of benefits and risks of a practice or a drug. With available knowledge, it is difficult to predict which one of the two children (NNTP = 2) will benefit with the prophylactic ondansetron (table 3). Risk-predictive scoring in children, as we have for adults,[17] in this regard might be useful to further improve efficiency of prophylactic ondansetron.

Although elevation of liver enzymes caused by ondansetron on the fifth or sixth postoperative day has been stated as a significant risk,[2,18–20] its clinical relevance compared with placebo is unknown.[2] No study in children with ondansetron to prevent PONV has measured the levels of liver enzymes. We could not measure the levels of liver enzymes because our patients were discharged on the first postoperative day. Moreover, our study did not provide an ideal setting in which to measure levels of liver enzymes because we used halothane intraoperatively. Although headaches are reported to be a significant side effect of ondansetron,[2] they were not severe in nature and either resolved with simple analgesics or did not necessitate any treatment.[21] In our trial, the NNTHs for headache in the 75- and 100-μg/kg ondansetron groups were infinity, indicating no extra harm with ondansetron compared with placebo; NNTH in the 150-μg/kg ondansetron group was 30, causing headache in 1 in 30 children (table 3). This observation is unlikely to have a clinical significance for the safety of ondansetron because it is an isolated observation from our study, which had a relatively small sample size for showing differences between ondansetron groups. We could not assess another nonsurrogate measure, unexpected admissions to the hospital because of PONV after discharge because all of our patients were observed in hospital for 24 h.

The occurrence and importance of PONV after discharge at home after ambulatory surgery have been underestimated because patients are not under the direct care of a health professional.[22] PONV after strabismus repair tends to occur after 2–8 h rather than in the immediate postoperative period.[23] In this trial, we used the opportunity of 24-h inpatient care to confirm the

same with a similar observation. Many children undergoing squint repair as an ambulatory procedure therefore have to cope with PONV when traveling or at home.[23] PONV may delay discharge or lead to unanticipated hospital admission,[24] increasing the direct cost to hospital and patients. Although the provider cost has been reduced with ambulatory surgery, a significant portion of the cost and impact of this care has been shifted to the patient or family.[25] Methods to reduce the incidence of PONV could result in increased hospital efficiency, improved quality of health care, and possibly reduced cost to hospitals.[22]

The main concern about this study is the timing of ondansetron administration. Ondansetron may be more effective if administered at the end of the surgery.[26] It did not seem appropriate to alter the study design in the middle of this relatively large study because of a previous study on a different group of adult patients undergoing otolaryngologic surgery. Moreover, in our study, the average surgical time was almost half that of the trial,[26] which might significantly decrease the difference in the incidences of PONV, if it at all exists, between ondansetron administration at the beginning and the end of the strabismus surgery in children.

Patient comfort or satisfaction is one of the most important true outcome measures. If we aim for total elimination of "unpleasant" PONV, any improvement in patient satisfaction with prophylactic antiemetics is a worthwhile step toward the goal. Perioperative drug (ondansetron) cost containment should no longer be an option to achieve the goal of improved patient outcome and comfort; rather it might be a necessity to significantly reduce the global cost of care. In this study, we found that prophylactic ondansetron at doses of 75 μg/kg or more was effective in reducing the incidence of PONV and duration of PACU stay and in improving the comfort after strabismus repair in children. In this era of evidence-based medicine, this trial shows that routine use of prophylactic ondansetron (≥ 75 μg/kg) improves perioperative outcome in children undergoing strabismus repair. Our observation is in accordance with a recent evaluation of three multicenter clinical trials that justified the use of prophylactic ondansetron in patients at a higher risk of PONV undergoing ambulatory surgery, including strabismus surgery, even at a higher cost, because of its benefits in terms of effectiveness and safety.[27]

In conclusion, for strabismus repair in children, which carries a very high risk of PONV, after analyzing clinically and therapeutically meaningful outcome measures, we justify the practice of routine prophylactic ondansetron until there is a safer, better, and more cost-effective alternative. Ondansetron 75 μg/kg is as effective as 150 μg/kg in solving this big "little" problem.

References

1. Fisher DM: The "big little problem" of postoperative nausea and vomiting: Do we know the answer yet? ANESTHESIOLOGY 1997; 87: 1271-3

2. Tramer MR, Reynolds JM, Moore RA, McQuay HJ: Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: A quantitative systematic review of randomized, placebo-controlled trials. ANESTHESIOLOGY 1997; 87:1277-89

3. Holliday MA, Seegar WE: The maintenance need for water in parenteral fluid therapy. Pediatrics 1957; 19:823-32

4. Aldrete JA, Kroulik D: A postanesthetic recovery score. Anesth Analg 1970; 49:924-34

5. Abramowitz MD, Oh TH, Epstein BS, Ruttimann UE, Friendly DS: The antiemetic effect of droperidol following outpatient strabismus surgery in children. ANESTHESIOLOGY 1983; 59:579-83

6. Hardy JF, Charest J, Girouard G, Lepage Y: Nausea and vomiting after strabismus surgery in pre-school children. Can Anaesth Soc J 1986; 33(1):57-62

7. Lin DM, Furst SR, Rodarte A: A double-blinded comparison of metoclopramide and droperidol for prevention of emesis following strabismus surgery. ANESTHESIOLOGY 1992; 76(3):357-61

8. Watcha MF, Bras PJ, Cieslak GD, Pennant JH: The dose-response relationship of ondansetron in preventing postoperative emesis in pediatric patients undergoing ambulatory surgery. ANESTHESIOLOGY 1995; 82:47-52

9. Watcha MF, Safavi FZ, McCulloch DA, Tan TS, White PF: Effect of antagonism of mivacurium-induced neuromuscular block on postoperative emesis in children. Anesth Analg 1995; 80:713-7

10. Joshi GP, Garg SA, Hailey A, Yu SY: The effects of antagonizing residual neuromuscular blockade by neostigmine and glycopyrrolate on nausea and vomiting after ambulatory surgery. Anesth Analg 1999; 89: 628-31

11. Tramer MR, Fuchs-Buder T: Omitting antagonism of neuromuscular block: Effect on postoperative nausea and vomiting and risk of residual paralysis. A systemic review. Br J Anaesth 1999; 82:371-3

12. Shende D, Mandal NG: Efficacy of ondansetron and metoclopramide for preventing postoperative emesis following strabismus surgery in children. Anaesthesia 1997; 52:489-500

13. White PF, Watcha MF: Has the use of meta-analysis enhanced our understanding of therapies for postoperative nausea and vomiting? Anesth Analg 1999; 88:1200-2

14. Cook RJ, Sackett DL: The number needed to treat: A clinically useful measure of treatment effect. BMJ 1995; 310:452-4

15. Laupacis A, Sackett DL, Roberts RS: An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988; 318(26):1728-33

16. Furst SR, Sullivan LJ, Soriano SG, McDermott JS, Adelson PD, Rockoff MA: Effects of ondansetron on emesis in the first 24 hours after craniotomy in children. Anesth Analg 1996; 83:325-8

17. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N: A simplified risk score for predicting postoperative nausea and vomiting: Conclusions from cross-validations between two centers. ANESTHESIOLOGY 1999; 91:693–700

18. Leeser J, Lip H: Prevention of postoperative nausea and vomiting using ondansetron, a new, selective, 5-HT_3 receptor antagonist. Anesth Analg 1991; 72:751–5

19. Sung YF, Wetchler BV, Duncalf D, Joslyn AF: A double-blind, placebo-controlled pilot study examining the effectiveness of intravenous ondansetron in the prevention of postoperative nausea and emesis. J Clin Anesth 1993; 5(1):22–9

20. Helmers JH: Oral ondansetron in the prevention of postoperative nausea and vomiting. Eur J Anaesthesiol 1992; 9(suppl 6):49–54

21. Rust M, Cohen LA: Single oral dose ondansetron in the prevention of postoperative nausea and emesis. Anaesthesia 1994; 49(suppl): 16–23

22. Hirsch J: Impact of postoperative nausea and vomiting in the surgical setting. Anaesthesia 1994; 49(suppl):30–3

23. Kenny GNC: Risk factors for postoperative nausea and vomiting. Anaesthesia 1994; 49(suppl):6–10

24. Patel RI, Hannallah RS: Anesthetic complications following pediatric ambulatory surgery: A 3-yr study. ANESTHESIOLOGY 1988; 69: 1009–12

25. Swan BA, Maislin G, Traber KB: Symptom distress and functional status changes during the first seven days after ambulatory surgery. Anesth Analg 1998; 86:739–45

26. Sun R, Klein KW, White PF: The effect of timing of ondansetron administration in outpatients undergoing otolaryngologic surgery. Anesth Analg 1997; 84:331–6

27. Pearman MH: Single dose intravenous ondansetron in the prevention of postoperative nausea and vomiting. Anaesthesia 1994; 49(suppl):11–5