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Low-dose Ondansetron with Dexamethasone More Effectively Decreases Vomiting after Strabismus Surgery in Children than Does High-dose Ondansetron

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Background: **Ondansetron and dexamethasone have been observed to decrease the incidence of vomiting by children after general anesthesia. This study compared the effect of high-dose (150 μg/kg) ondansetron with low-dose (50 μg/kg) ondansetron plus 150 μg/kg dexamethasone on the incidence of vomiting after strabismus in children.**

Methods: **This study had a double-blind, blocked, stratified, randomized design. With parental consent and Hospital Ethics Committee approval, healthy children aged 2–14 yr who were undergoing elective strabismus surgery were studied. Anesthesia was induced intravenously with propofol or by inhalation with halothane and nitrous oxide. Patients in the high-dose group were given placebo plus 150 μg/kg (maximum dose, 8 mg) of ondansetron intravenously, whereas patients in the low-dose group were given 150 μg/kg dexamethasone (maximum dose, 8 mg) and 50 μg/kg ondansetron intravenously in a double-blind manner. Anesthesia was maintained with halothane and nitrous oxide. All incidences of vomiting occurring as long as 24 h after anesthesia were recorded.**

Results: **Three of the 200 patients enrolled in the study were excluded from data analysis. The groups were similar with respect to demographic data and potential confounding variables. Patients vomited from 0–12 times. The low-dose ondansetron plus dexamethasone group had a lower incidence of vomiting, 9% (95% CI = 4–17%) *versus* 28% (95% CI = 20–38%; $P < 0.001$). Only 1% of the patients in the low-dose ondansetron plus dexamethasone group vomited while in the hospital.**

Conclusions: **Low-dose ondansetron plus dexamethasone is an effective prophylactic antiemetic combination for children undergoing strabismus surgery. (Key words: Ambulatory surgery; antiemetic; costs.)**

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VOMITING is frequently an unpleasant consequence of general anesthesia among children. Vomiting may lead to marked physiologic derangements, delayed hospital discharge, or unscheduled admission to the hospital.[1-7]

Anesthesiologists are searching for anesthetic techniques and drugs that will minimize vomiting after surgery. Ondansetron, a relatively expensive antiemetic, has been shown to decrease postoperative vomiting by children.[8] Different doses of ondansetron have been studied. When high-dose (150 μg/kg) ondansetron was compared with low-dose (50 μg/kg) ondansetron, it was noted that high-dose ondansetron was a more effective prophylactic antiemetic, especially after discharge from the hospital.[3]

Dexamethasone has antiemetic properties and an elimination half-life of about 3 h and a duration of action of 48 h. Among patients receiving chemotherapy, dexamethasone was superior in suppressing delayed nausea when compared with either ondansetron or granisetron.[9,10] Perioperatively, dexamethasone has been shown to decrease the incidence of postoperative vomiting.[4,11-13]

It was hypothesized that the relatively expensive high-dose ondansetron would have the same effect on vomiting after strabismus surgery in children as low-dose ondansetron plus 150 μg/kg dexamethasone.

Materials and Methods

Healthy children aged 2-14 yr undergoing elective strabismus surgery were enrolled in this double-blind, blocked, stratified, randomized study with parental consent and hospital ethics committee approval. Patients were excluded from the study if they had an allergy to any of the drugs to be used or they had a symptomatic medical illness.

Premedication with 0.5 mg/kg midazolam given orally

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20–30 min before operation was ordered when indicated. When the patient arrived in the operating room, baseline hemodynamic data were recorded after placement of routine monitors. After sedation with nonanesthetic levels of nitrous oxide, anesthesia was induced intravenously with 2.5–3.5 mg/kg propofol + 0.5 mg/kg lidocaine or with inhalation anesthesia with halothane and nitrous oxide. After induction, an endotracheal tube or laryngeal mask airway was placed under the appropriate depth of anesthesia. Mivacurium (0.25 mg/kg) was administered only if a muscle relaxant to facilitate tracheal intubation was indicated. Before randomization using a computer-generated random number table, the patients were stratified according to potential confounding variables, including the number of muscles to be operated on, premedication, and induction technique. The patients in the high-dose group received placebo plus 150 μg/kg (maximum dose, 8 mg) ondansetron intravenously, and the patients in the low-dose group received 150 μg/kg dexamethasone (maximum dose, 8 mg) and 50 μg/kg ondansetron intravenously in a double-blind fashion. All patients were given 20 μg/kg atropine intravenously. Anesthesia was maintained with 70% nitrous oxide and 0.75–2.0% halothane. Intraoperative intravenous fluids were Ringer's lactate at standard rates. Standard rates were defined as one half of the deficit during the first hour, plus maintenance fluids.

For the purpose of this study, vomiting was defined as the forceful expulsion of liquid or solid gastric contents. Retching was not considered vomiting. Postoperative vomiting was treated with 1 mg/kg dimenhydrinate given intravenously if the patient vomited twice. The incidence of vomiting in the hospital was recorded by the nursing staff. Postoperative pain was treated with 10–15 mg/kg acetaminophen elixir given orally. Ringer's lactate was administered intravenously at twice maintenance rates after surgery. Patients were monitored for a minimum of 1 h in the day care surgical unit after an initial recovery in the postanesthesia care unit.

Parents were interviewed on the day after surgery by the research assistant. The parents reported all episodes of vomiting and any other potential surgical or anesthesia-related problems.

Sample size was determined by assuming that the overall incidence of vomiting would be 30%, and we considered it clinically significant if one group had a 20% greater incidence. The alpha error was set at 0.05 and Type II error was set at 0.20. The projected sample size was 100 patients per group.

Table 1. Demographic Data

	50 μg/kg Ondansetron Plus Dexamethasone	150 μg/kg Ondansetron
Number of patients	99	98
Age (yr)	6.5 ± 3.1	6.1 ± 2.7
Weight (kg)	24 ± 13	22 ± 8
Premedication (n)	24	22
Intravenous induction (n)	45	41
Number of muscles (n)	39	39
1		
2	58	56
3 or 4	2	3
Anesthesia time (min)	56 ± 23	59 ± 23
Mivacurium given (n)	34	29
PACU time (min)	44 ± 14	41 ± 11
DCSU time (min)	80 (53–240)	75 (45–165)

Values listed are n or mean ± SD of median (range). PACU = post-anesthesia care unit room; DCSU = day care surgical unit.

Age, weight, and other normally distributed data were compared with one-way analysis of variance. Nonparametric data were compared using the Mann-Whitney U test. Sex and other nominal data were compared with chi-square analysis or Fisher exact tests, whichever was appropriate. The relation between the incidence of vomiting and the study intervention plus other potential confounders (age, weight, premedication, induction technique, airway management, number of muscles operated on, anesthesia time, and postoperative analgesic use) was evaluated with logistic regression analysis.

Results

Two hundred patients were enrolled; three patients were excluded from data analysis because of protocol violations. The groups were similar with respect to demographic data, including in-hospital acetaminophen use (table 1).

Patients vomited from 0–12 times. The low-dose ondansetron plus dexamethasone group had a lower incidence of vomiting, at 9% (95% CI = 4–17%) *versus* 28% (95% CI = 20–38%; $P < 0.001$; table 2). Overall only eight (4%) patients vomited while in the hospital, and this lack of emesis was less in the low-dose group, in which only one (1%) patient vomited while in the hospital (table 2). Excessive vomiting (three or more episodes of vomiting) was more common in the high-dose ondansetron group at 13% compared with 2% ($P < 0.05$). The two confounders that had a significant

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Table 2. Postoperative Vomiting

	Low-dose Ondansetron Plus Dexamethasone	High-dose Ondansetron
Vomiting		
In-hospital	1%	7%*
PACU	0%	3%
DCSU	1%	4%
Out-of-hospital	9%	24%*
Day of surgery	7%	14%
Next Day	5%	15%*
Overall	9%	28%†

PACU = post-anesthetic care unit; DSCU = day care surgical unit.

* $P < 0.05$.

† $P < 0.001$.

effect by logistic regression analysis on the incidence of vomiting were patient age ($P = 0.01$, the incidence of vomiting increased with age) and number of muscles operated on ($P = 0.01$, the incidence of vomiting increased with the number of muscles operated on). In addition, 17% of the children who had a premedicant vomited after surgery, whereas 19% of those who did not receive a premedicant vomited ($P = 0.58$). Also, 22% of the children who had an intravenous induction had postoperative emesis ($P = 0.08$). The children who received mivacurium or had a laryngeal mask airway inserted had nearly identical incidences of vomiting (19% *vs.* 20%) when compared with those who did not receive mivacurium or have an laryngeal mask airway inserted.

Vomiting, although uncommon, affected patient care. One patient was readmitted to the hospital because of excessive vomiting. In addition, the parents of three children sought medical help for management of vomiting more than 10 times. Vomiting prolonged in-hospital length of stay by 19 ± 11 min ($P = 0.08$). Thirteen patients received a rescue antiemetic (dimenhydrinate), eight of whom were in the high-dose group.

Discussion

We observed unexpectedly that low-dose ondansetron plus dexamethasone was a more effective prophylactic antiemetic when compared with high-dose ondansetron. Thus the study's null hypothesis was rejected because the two study groups had unequal results. The combination of low-dose ondansetron plus dexamethasone had a rather remarkable effect on minimizing vomiting after strabismus surgery in children. The 9% incidence of vomiting is markedly less than the rate observed after high-dose ondansetron and is, to the best of our knowledge, the lowest reported incidence after strabismus surgery in children. Of further note is the nearly total lack of in-hospital vomiting in the low-dose group.

We hypothesized that low-dose ondansetron would decrease in-hospital vomiting, whereas dexamethasone would decrease vomiting after discharge. This effect, plus more, was observed. Our findings suggest that this combination may be synergistic. Alternatively, dexamethasone alone may be an effective prophylactic antiemetic among children having strabismus surgery because there are no studies showing the effect or lack thereof of dexamethasone on vomiting after strabismus surgery in children.

Vomiting after anesthesia is an unappealing experience, but its clinical importance is not well established. All patients in the present study received a prophylactic antiemetic, and we believe this was appropriate. Prophylactic antiemetics in the current study model decrease vomiting among a group of patients at high risk for adverse events from vomiting. These adverse events include unexpected admission and delayed discharge.[5–7] Fortunately, severe physiologic adverse events, such as death, are rare.[1]

The current study had a balanced design to control for potential confounding variables, such as number of muscles operated on, premedication, and induction technique. This design still allows for optimal clinical care within the structure of a study. Alternatively, the study design could have been more rigid, but then the results would have been less applicable to common clinical practice. Even with such a "flexible" method, the results are only relevant to children undergoing strabismus surgery.

Cost is increasingly a focus in health care. High-dose ondansetron is not only less effective but more expensive than the combination of low-dose ondansetron plus dexamethasone. Currently, dexamethasone costs only $1.00 (in Canadian currency) for 20 mg, whereas ondansetron costs $86.00 for 20 mg at our hospital. Which combination of dexamethasone and ondansetron is the most cost-effective is not known. In the present study, 50 μg/kg ondansetron was used, but a lower, less-expensive dose may be comparably effective. In addition to lower drug costs, the low-dose ondansetron plus dexamethasone group was likely associated with lower nursing costs, because of markedly less vomiting (1% in-hospital) and less excessive vomiting (2% for the low-

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dose group compared with 13% for the high-dose group).

Investigations of the perioperative use of dexamethasone are surprisingly uncommon. Research in oncology patients demonstrates its efficacy with minimal adverse events.[9,10] McKenzie *et al.*[11] observed that the combination of ondansetron plus dexamethasone was more effective than ondansetron with placebo in preventing vomiting for women after major gynecologic surgery. Caitlin and Grimes[12] compared the effect of dexamethasone to placebo on recovery from tonsillectomy in 25 children. This small number of patients was followed for 1 week and evaluated for pain, emesis, fever, and appetite. The two groups were similar, except that the 10 patients in the dexamethasone-treated group had a more rapid return to their normal diet. Baxendale *et al.*[13] observed that dexamethasone decreased pain, swelling, and vomiting after extraction of third molars in adults.[13] In addition, dexamethasone, when compared with placebo, markedly decreased the incidence of vomiting after tonsillectomy in children.

The mechanism of antiemetic action of dexamethasone is unknown. Whether similar antiemetic effects would be observed after alternative systemic steroids is not well established. The antiemetic dose of dexamethasone used in children is not well established. Based on this and similar studies, a dose of about 150 μg/kg up to 8 mg appears to be effective.[4,12] Whether a lower dose would be as effective or whether a larger dose would be more effective is unknown.

Adverse effects with a single dose of dexamethasone are probably extremely rare and minor in nature. Many patients have received dexamethasone at our hospital perioperatively without any adverse effect observed by any of the investigators. A review of a United States Pharmacopeia Drug Information handout and a literature search revealed no reports of a side effect associated with the use of a single dose of dexamethasone.

In summary, 50 μg/kg ondansetron plus 150 μg/kg dexamethasone more effectively decreases the incidence and severity of vomiting by children after strabismus surgery than does 150 μg/kg ondansetron.

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