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Metoclopramide Reduces the Incidence of Vomiting Following Strabismus Surgery in Children

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This randomized, double-blind study evaluated the efficacy of metoclopramide administered at the completion of surgery as an antiemetic agent in pediatric patients undergoing ambulatory strabismus surgery; 126 unpremedicated ASA Physical Status 1 and 2 children ranging in age from 2 to 18 yr served as subjects. All received general anesthesia with halothane, N_2O, and O_2; tracheal intubation was facilitated with intravenous (iv) atracurium 0.5 mg/kg. Intravenous atropine 0.02 mg/kg and lactated Ringer's solution with 5% dextrose equivalent to 4 h of maintenance fluids were administered during surgery. Neither opioids nor droperidol were given intraoperatively. At the completion of surgery, residual muscle paralysis was reversed with atropine 0.02 mg/kg (maximum dose 1.0 mg) and neostigmine 0.07 mg/kg (maximum dose 5.0 mg), and the stomach was decompressed prior to tracheal extubation. After the patient had been transferred to the postanesthesia recovery room (PARR) either metoclopramide 0.15 mg/kg or normal saline was administered intravenously to the children over a 1-min period. A research associate monitored the children for the incidence of postoperative vomiting and the time required for each child to meet discharge criteria from Short Stay Recovery Unit (SSRU). If a child vomited more than three times in both the PARR and SSRU, the vomiting was construed to be severe and the patient was offered further antiemetic treatment with iv droperidol 70 μg/kg. The incidence of postoperative vomiting in the metoclopramide group was 37% *versus* 59% in the placebo group ($P < 0.05$). The time required for children who received metoclopramide to meet standard discharge criteria was 207.4 ± 60.0 min (range, 100–425 min), whereas that for controls was 248.8 ± 84.5 min (range, 110–480 min). This difference is also statistically significant ($P < 0.002$). Eight children who received the placebo required adjunct antiemetic therapy for protracted postoperative vomiting. None of the children who received metoclopramide had protracted or severe postoperative nausea and vomiting. This difference in the incidence of severe postoperative nausea and vomiting was statistically significant ($P < 0.006$). Finally, there were no adverse reactions to either metoclopramide or placebo, and none of the children appeared to be drowsy or sedated. (Key words: Anesthesia: pediatrics. Antiemetics: metoclopramide. Complications: postoperative vomiting. Surgery: strabismus.)

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THERE IS a high incidence of postoperative nausea and vomiting in children undergoing strabismus surgery. Furthermore, persistent postoperative nausea and vomiting may significantly delay the patient's discharge from the ambulatory surgical unit.

Droperidol, 75 μg/kg, administered either before or during surgery has been shown to be an effective antiemetic in children undergoing strabismus surgery on an ambulatory basis.[1,2] However, it has been our experience at Children's National Medical Center (CNMC) that 75 μg/kg droperidol may produce profound and protracted somnolence, which may delay discharge or prompt an occasional unscheduled hospital admission. Metoclopramide is an antiemetic drug with a relatively short duration of action and does not produce sedation.[3] In addition to its central antiemetic properties, metoclopramide has been shown to accelerate gastric emptying and to increase lower esophageal sphincter tone.[4]

We evaluated the efficacy of metoclopramide administered prophylactically at the completion of surgery as an antiemetic agent in pediatric patients undergoing ambulatory strabismus surgery.

Materials and Methods

Permission to conduct this randomized, double-blind study was obtained from the hospital's institutional review committee. Informed consent was obtained from the parents of 126 ASA Physical Status 1 and 2 children, ages 2–18 yr, who were undergoing elective strabismus surgery on an ambulatory basis. Patients predisposed to nausea and vomiting secondary to gastrointestinal reflux, gastroparesis, motion sickness, inner ear disorders, or CNS disorders were excluded. None of the children received preoperative medication. All children were prohibited from eating solid food or drinking milk products after midnight on the evening prior to surgery. However, children younger than 5 yr of age were permitted to consume clear liquids up to 6 h prior to surgery. Following induction of general anesthesia with either intravenous (iv) thiamylal or inhaled halothane, N_2O, and O_2, all children received iv 0.02 mg/kg atropine (maximum dose, 1.0 mg). Tracheal intubation was facilitated with iv 0.5 mg/kg atracurium and anesthesia was maintained with N_2O, O_2, and halothane. Neither opioids nor droperidol was given intraoperatively to any patient. An iv bolus of lactated Ringers' solution with 5% dextrose corresponding to four

times the calculated hourly maintenance rate was infused during each surgical procedure. Following completion of the surgical procedure residual muscle paralysis was antagonized with 0.02 mg/kg atropine (maximum dose, 1.0 mg) and 0.07 mg/kg neostigmine (maximum dose, 5.0 mg), and the stomach was decompressed prior to tracheal extubation. After the patient was transferred to the postanesthesia recovery room (PARR) and it had been determined that vital signs were stable, either 0.15 mg/kg metoclopramide or normal saline was administered intravenously to the children over a 1-min period. Both solutions were supplied by the pharmacy in a numbered vial and administered in a double-blind fashion.

A research associate, independent from the nursing team, monitored the children for the incidence of vomiting from the time of admission to PARR until discharge from the short stay recovery unit (SSRU). Vomiting was defined as the active expulsion of a measurable amount of gastric contents. Retching, which did not result in the expulsion of gastric contents, was not included. The time required for each child to meet predetermined PARR and SSRU discharge criteria was also noted. If a child vomited more than three times in both the PARR and SSRU, the vomiting was construed to be severe and the patient was administered further antiemetic treatment with iv 70 μg/kg droperidol.

The effect of metoclopramide on the incidence of vomiting was investigated by a restricted sequential decision plan.[5] This experimental design was used in a previous study to show that 75 μg/kg droperidol administered intraoperatively could reduce the incidence of postoperative vomiting from 85% in the placebo control group to 43% in the treatment group ($P < 0.05$).[1] Therefore, in the design of the current study we hypothesized that there would be a comparable decrease in the incidence of vomiting following metoclopramide therapy. We also assumed that the incidence of vomiting in the control group would be 70% based upon the incidence of postoperative vomiting observed in the control groups of similar studies.[1,2,6,7] A decrease of this incidence rate to 40% or less after metoclopramide administration was considered to be clinically relevant, and it was desired that this be detected with $P = 0.05$, if present, with a power of 0.95. This design was expected to require a maximum of 62 untied patient pairs. One patient of each pair received 0.15 mg/kg metoclopramide and the other received a placebo in a double-blind, randomized pattern. The response criterion for the decision to stop the trial was when the difference in the number of observed preferences in the formed pairs reached statistical significance either toward metoclopramide or placebo (fig. 1).

Age and weight differences between the two treatment groups were analyzed for statistical significance by the *t* test, and sex distributions were compared by the chi-square test. Because the data were not normally distributed, Wilcoxon's rank-sum test was used to determine differences between discharge times for the metoclopramide treatment group *versus* the placebo group and for children vomiting or not vomiting, regardless of their treatment modality. The difference between the incidence of droperidol administration to patients with severe vomiting in the placebo and metoclopramide treatment groups was analyzed using Fisher's exact test. A P value of < 0.05 was considered to be statistically significant in all tests.

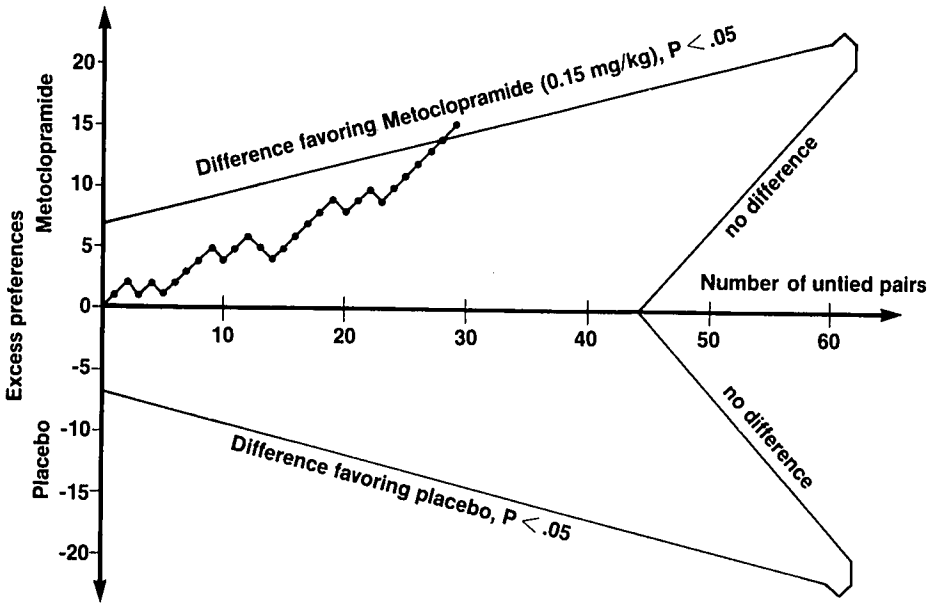

FIG. 1. Sequential analysis chart to compare metoclopramide *versus* placebo group, using a restricted plan with $P = 0.05$, and power = 0.95. The design requires a maximum of 62 untied patient pairs.

Results

Statistical significance with a preference for metoclopramide was reached after 62 sequential patient pairs were obtained; two patients in the placebo group were left unmatched (n = 126). This resulted in 29 untied observation pairs with 22 in favor of metoclopramide and seven in favor of the placebo (fig. 1). Among the 33 tied pairs both patients vomited in 15 pairs and in 18 pairs neither patient vomited. One of the two unmatched patients in the placebo group vomited; the other did not. There were no statistically significant differences in the mean ages, weights, or the sex distribution of the children in the metoclopramide and placebo groups (table 1). The incidence of postoperative vomiting in the metoclopramide group was 35% *versus* 59% in the placebo group. This difference is statistically significant ($P < 0.05$). Children who received metoclopramide reached discharge criteria earlier [207.4 ± 60.0 min (range, 100–425 min)] than those given placebo [248.8 ± 84.5 min (range, 110–480 min)] ($P < 0.002$). There were no adverse reactions to either metoclopramide or placebo, and none of the children subjectively appeared to be drowsy or sedated. Children who vomited, regardless of the treatment modality, required 275.3 ± 78.0 min to meet SSRU discharge criteria compared with 184.4 ± 39.1 min for those who did not vomit ($P < 0.001$). Finally, eight children vomited three or more times in PARR and SSRU, and all of them were treated with iv 70 μg/kg droperidol. All of these children had received the placebo. None of the children who received metoclopramide had severe postoperative nausea and vomiting. This difference in the incidence of severe postoperative nausea and vomiting was statistically significant ($P < 0.006$).

TABLE 1. Demographic Data

	Placebo	Metoclopramide	Statistical Significance (P)
N	64	62	
Age (mo) ± SD	76.4 ± 46.8	70.1 ± 43.1	>0.4*
Weight (kg) ± SD	23.9 ± 14.2	22.4 ± 13.1	>0.5*
Sex (male/female)	34/30	35/27	>0.7†

* *t* test.
† Chi-square test.

Discussion

The incidence of postoperative vomiting following strabismus surgery in children who have not received some form of prophylactic antiemetic treatment has been reported to range from 46% to 85%.[1,2] This incidence is higher than that associated with other pediatric ambulatory surgical procedures in which similar anesthetic techniques were employed.[1] Droperidol and promethazine have been evaluated for postoperative antiemetic efficacy in this patient population and have been shown to significantly reduce the incidence of postoperative nausea and vomiting.[1,2,6] Data regarding the antiemetic efficacy of lidocaine show both benefit and lack of benefit.[7,8]

Droperidol has been reported extensively as an effective antiemetic in the perioperative period.[1-3,6,9-11] Its beneficial effects have been demonstrated in children undergoing strabismus surgery as well as various other procedures. However, hospital discharge may be delayed when droperidol is used in a clinically effective dose range because of its inherent sedative properties.[1,3,12] Abramowitz *et al.*[1] showed that children in their placebo group who did not vomit were discharged 73 min earlier than nonvomiting children who had received droperidol. This difference was statistically significant. Cohen *et al.*[3] showed that droperidol significantly delayed recovery in a group of adult women undergoing therapeutic abortion. The same study showed that patients who received metoclopramide sat, walked, and were discharged earlier than either the droperidol or control group. We noted similar results with metoclopramide in our study. The metoclopramide group in our study experienced no postoperative sedation and had a significantly shorter discharge time than did controls. However, the administration of adjunct antiemetic agents, such as droperidol, may produce somnolence and further delay discharge.

Studies in adults have shown that both timing of metoclopramide administration and total dosage may be important variables in reducing the incidence of postoperative vomiting. Clark and Storrs showed that 20 mg metoclopramide (~0.3 mg/kg) administered intramuscularly after the evacuation of the uterus following incomplete abortion was significantly more effective in reducing the incidence of postoperative nausea and vomiting than was a placebo.[13] However, Cohen *et al.*[3] were unable to demonstrate that 10 mg metoclopramide (~0.15 mg/kg) was any more effective than a placebo when administered intravenously 2–10 min prior to the induction of anesthesia for therapeutic abortions.

The recommended metoclopramide dose for children younger than 14 yr of age is 0.1 mg/kg not to exceed $0.5\ mg \cdot kg^{-1} \cdot (day)^{-1}$.[4] However, members of the oncology department at CNMC routinely employ 10–15 times this dose (metoclopramide, 1.0–1.5 mg/kg) as prophylaxis against cisplatin-induced emesis. The only adverse side effects noted in these children have been drowsiness and extrapyramidal reactions, and the latter are easily reversed with diphenhydramine. In the present study we chose a dose similar to that employed by Cohen *et al.*[3] (0.15 mg/kg) but greater than is recommended for children in the package insert (0.1 mg/kg). The half-life of intravenously administered metoclopramide is only 2.6–4.6 h in adults.[4] Because of the brief duration of action of metoclopramide,

we chose to administer it at the completion of surgery. Clearly, further work needs to be done to establish the optimal time for metoclopramide administration and the possible benefit of employing higher doses of the drug to further reduce the incidence of postoperative nausea and vomiting in children.

Minor adverse side effects, such as drowsiness and irritability, have been noted in neonates receiving metoclopramide (0.5 $mg \cdot kg^{-1} \cdot [day]^{-1}$) for gastroesophageal reflux.[14] Inadvertent overdosages have been reported in two neonates receiving metoclopramide (1.0 mg/kg).[14,15] One developed an oculogyric crisis;[14] the other developed methemoglobinemia.[15] Both of these iatrogenic overdoses were successfully treated, the former with diphenhydramine and the latter with methylene blue.

Metoclopramide not only reduces the incidence of postoperative vomiting and speeds discharge but also attenuates the severity of postoperative vomiting; none of the children in our study who received metoclopramide had severe postoperative vomiting. The ability of metoclopramide to attenuate the severity of vomiting following strabismus surgery may be as important as its ability to reduce the incidence of vomiting per se.

Metoclopramide probably reduces postoperative nausea and vomiting through several mechanisms; like droperidol, it is a dopamine antagonist. The antiemetic effects of these drugs are probably mediated, at least in part, by blockade of dopamine receptors in the chemoreceptor trigger zone.[4] Although both drugs have been show to reduce the incidence of vomiting following strabismus surgery to about 40% when administered at the completion of surgery, metoclopramide, in contrast to droperidol, does not produce drowsiness and does not delay discharge.[1,3,13] In addition, metoclopramide probably has several other mechanisms of antiemetic action. It is known to increase lower esophageal sphincter tone and is probably also active through acetylcholine receptors.

The most important peripheral antiemetic effect of metoclopramide may be its ability to increase gastric motor activity. This effect probably prevents gastric relaxation, which must precede the act of vomiting.[4] Atropine is usually employed as an adjunct agent in anesthesia for pediatric strabismus surgery. However, anticholinergics have been shown to antagonize the gastric stimulatory effects of metoclopramide.[16] Preanesthetic medication with atropine and the use of atropine in conjunction with anticholinesterase agents may reduce the antiemetic efficacy of metoclopramide by blocking the metoclopramide-induced inhibition of gastric relaxation that must precede vomiting. The interaction of these two drugs, atropine and metoclopramide, in this setting warrants further investigation.

In summary, we have shown that metoclopramide (0.15 mg/kg), administered at the completion of strabismus surgery, significantly reduces the incidence of postoperative vomiting, shortens discharge times, and attenuates the severity of vomiting in unpremedicated children. No adverse reactions were noted with either metoclopramide or placebo.

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