William M. Splinter MD FRCPC,
Elliot J. Rhine MB CHB FRCPC,
David J. Roberts MD FRCPC

Vomiting after strabismus surgery in children: ondansetron *vs* propofol

Purpose: To compare the antiemetic efficacy and costs associated with two anaesthetic regimens in children undergoing strabismus surgery. One regimen contained halothane, nitrous oxide and ondansetron, while the other contained propofol and nitrous oxide.

Methods: Three hundred children aged 2–14 yr undergoing strabismus surgery were enrolled into this single-blind, randomized, stratified, blocked study with a balanced design. Anaesthesia was induced by inhalation with halothane/N₂O/O₂ (Group O) or with 2.5–3.5 mg·kg⁻¹ propofol + 0.5 mg·kg⁻¹ lidocaine iv (Group P). Group O patients were administered 0.15 mg·kg⁻¹ ondansetron (maximum dose 8 mg) iv and all patients received atropine 20 µg·kg⁻¹ iv immediately after induction of anaesthesia. Anaesthesia was maintained with N₂O and halothane (Group O) or N₂O and propofol (Group P). Patients were followed for 24 hr after their operation primarily to assess the incidence of postoperative vomiting. For each case, the costs of the anaesthetic drugs administered and their associated intravenous administration tubing were determined. Drug costs were those prevailing at the study site at the time of the investigation. Fixed costs, such as the cost of the anaesthetic equipment were not assessed.

Results: Groups were similar with respect to demographic data. The incidence of vomiting in both groups was 11% while in-hospital and 23% after discharge. Each episode of in-hospital vomiting prolonged discharge by 17 ± 4 min, $P < 0.001$. Mean cost per case for anaesthetic drugs was less in Group O, 18 ± 8 vs 21 ± 10 CDN\$, mean ± SD, $P < 0.01$.

Conclusion: The two methods of antiemetic prophylaxis were equally effective. Propofol-based anaesthesia was more expensive.

Objectif : Comparer l'efficacité antiémétique et les coûts associés à deux techniques anesthésiques chez des enfants opérés pour une correction de strabisme. Une des techniques comportait de l'halothane, du protoxyde d'azote, et de l'ondansetron, alors que l'autre comportait du propofol et du protoxyde d'azote.

Méthodes : Cette étude à l'insu, aléatoire, stratifiée et bloquée avec subtest des cubes avec modèle équilibré groupait trois cents enfants de 2 à 14 ans soumis à une correction chirurgicale de strabisme. L'anesthésie était induite par l'inhalation d'halothane/N₂O/O₂ (Groupe O) ou l'injection iv de propofol 2,5–3,5 mg·kg⁻¹ + lidocaïne 0,5 mg·kg⁻¹ (groupe P). On a administré de l'ondansetron 0,15 mg·kg⁻¹ iv aux patients du groupe O (maximum 8 mg) et, à tous les patients, de l'atropine 20 µg·kg⁻¹ iv immédiatement après l'induction de l'anesthésie. Le protoxyde d'azote et l'halothane (Groupe O) et le propofol (Groupe P) ont servi au maintien de l'anesthésie. La surveillance anesthésique postopératoire était surtout orientée vers l'évaluation des vomissements. Dans chacun des cas, le coût des agents anesthésiques administrés et des tubulures utilisées pour leur administration ont été évalués. Le coût des agents était ceux qui étaient en vigueur localement et au moment de l'étude. Les coûts fixes comme ceux qui sont inhérents à l'équipement anesthésique n'ont pas été évalués.

Résultats : Les données démographiques étaient les mêmes pour les deux groupes. L'incidence des vomissements (11%) à l'hôpital et hors de l'hôpital (23%) était identique pour les deux groupes. Chaque épisode de vomissements intrahospitalier a prolongé le séjour à l'hôpital de 17 ± 4 min, $P < 0,001$. Le coût moyen des agents anesthésiques par patient était inférieur dans le groupe O, (18 ± 8 vs 21 ± 10 \$, moyenne ± ÉT, $P < 0,01$)

Conclusion : Ces deux méthodes ont la même capacité de prévention des vomissements. L'anesthésie à base de propofol coûte plus cher.

From the Department of Anaesthesia, Children's Hospital of Eastern Ontario and the University of Ottawa, 401 Smyth Road, Ottawa, Ontario, Canada.

Address correspondence to: Dr. W. Splinter; Phone: 613-737-231; Fax: 613-738-4815; E-mail: splinter@cheo.on.ca.

Presented in part at the 1996 Annual Meeting of the Canadian Anaesthetists' Society, Montreal, Canada.

Accepted for publication 27 April 1997.

VOMITING after general anaesthesia is common among children. This is especially true among those undergoing strabismus surgery where up to 85% of patients suffer from vomiting.¹ This emesis often represents a considerable burden to our patients, their parents and the health care system. Protracted vomiting has been noted to be the most common cause of unscheduled admission following paediatric day care surgery.² Anaesthetists are searching for techniques and drugs that will minimize vomiting after surgery.³

Ondansetron is among a new class of antiemetic drugs that have been developed to antagonize 5-hydroxytryptamine type 3 receptors selectively. This drug has had a dramatic impact on oncology services with a considerable decrease in nausea and vomiting and minimal side effects.⁴ However, pharmacy departments have noticed a marked effect on their budget. The 4 mg *iv* dose costs \$17.20 CDN at our institution and ondansetron is currently the second most expensive item on our pharmacy budget, if drugs for patients with cystic fibrosis are excluded. Ondansetron has been shown to decrease postoperative emesis by children.^{5,6} Postoperative emesis has been reduced following the administration of propofol.^{7,8} Propofol, like ondansetron, is an expensive drug.

Although both ondansetron and propofol have been studied independently and are superior to placebo antiemetics, they have not been adequately compared with each other. Tramer *et al.* compared ondansetron/inhalation anaesthesia to propofol anaesthesia for strabismus surgery.⁹ In their small study, 60 patients were divided into four groups and the 29% incidence of vomiting in the isoflurane/ondansetron group and 60% rate in the propofol/lidocaine group was not different.⁹ Gan *et al.* studied women undergoing major breast surgery.¹⁰ They observed a lower incidence of vomiting among the patients who received propofol for induction and maintenance of anaesthesia than in those receiving ondansetron-thiopentone-isoflurane anaesthesia.

The purpose of the current study was to compare the efficacy and costs of two anaesthetic regimens, with proven antiemetic efficacy, in healthy children undergoing strabismus surgery in an ambulatory care setting. It was hypothesized that the incidence of vomiting after ondansetron plus halothane would be similar to that after induction and maintenance of anaesthesia with propofol.

Methods

With parental consent and Hospital Research Ethics Committee approval, healthy children, aged 2–14 yr undergoing elective strabismus surgery were enrolled

in this single-blind, randomized, stratified, blocked study. Patients were excluded from this study if they had an allergy to one of the drugs to be used, a non-study anaesthetic technique was deemed necessary by the attending anaesthetist or the patient was ASA physical class III or greater.

The children were not allowed to ingest solid food on the day of surgery, but were permitted to ingest clear fluids up to three hours before anaesthesia. Before randomization with the use of a random number table, patients were blocked (10 patients per block) and stratified as to the number of muscles to be operated upon¹² and whether premedication was indicated to ensure a balanced design. Premedication was with 0.5 mg·kg⁻¹ midazolam *po* (maximum dose 20 mg) when required.

After routine monitors were applied and after sedation with non-anaesthetic concentrations of N₂O, anaesthesia was induced by inhalation with halothane/N₂O/O₂ (Group O) or with 2.5–3.5 mg·kg⁻¹ propofol + 0.5 mg·kg⁻¹ lidocaine *iv* (Group P). If a child in Group O refused inhalation induction of anaesthesia, anaesthesia was induced with propofol and lidocaine and their data were excluded from final analysis. Following induction, 80 µg·kg⁻¹ vecuronium or 0.2 mg·kg⁻¹ mivacurium was administered *iv* if a muscle relaxant was indicated and then an endotracheal tube was placed under the appropriate depth of anaesthesia. Patients undergoing brief procedures, < one hour, typically received mivacurium, while most of the others received vecuronium.

Before surgery began, Group O patients were given 0.15 mg·kg⁻¹ ondansetron (maximum dose 8 mg) *iv* over two minutes. Then, all patients were given 20 µg·kg⁻¹ atropine and 50 µg·kg⁻¹ midazolam *iv*. Patients who had received midazolam premedication, did not receive intraoperative midazolam. Anaesthesia was maintained with N₂O 70% and halothane 0.75–2.0% (Group O) or N₂O 70% plus propofol at an initial rate of 10 mg·kg⁻¹·hr⁻¹ (Group P). Halothane (Group O) and propofol (Group P) were titrated to achieve the appropriate level of anaesthesia, which was defined as no patient movement and normal systolic blood pressure. Neuromuscular blockade was maintained with boluses of 20 µg·kg⁻¹ vecuronium or 0.05 mg·kg⁻¹ mivacurium *iv*, when indicated. Intraoperative *iv* fluid was Ringer's Lactate at a rate to administer half the fluid deficit during the first hour, in addition to the hourly maintenance.

Residual neuromuscular blockade was reversed with atropine 0.02 mg·kg⁻¹ and 0.06 mg·kg⁻¹ neostigmine at the end of surgery and the endotracheal tube was removed at the appropriate level of anaesthesia.

Post-operative orders included: 1 mg·kg⁻¹ dimenhydrinate *iv* slowly, if the patient vomited twice; anaesthe-

sia to be notified if the patient vomited on four occasions; Ringer's Lactate *iv* at twice maintenance rates; discharge the patient using routine criteria after a minimum stay of 120 min in the Day Care Surgical Unit (DCSU); and 10–15 mg·kg⁻¹ acetaminophen elixir *po* for pain. Patients were not encouraged to drink clear fluids before discharge from DCSU.

Patients were followed for 24 hr after the operation. Parents recorded all emetic episodes and medications taken in a diary and were interviewed the day after surgery by a research assistant. Each chart and diary were reviewed by two research assistants to confirm the recorded data and compliance with study protocol. For the purpose of the study, vomiting was defined as the forceful expulsion of liquid gastric contents. Retching and nausea were not considered to be vomiting. Nursing staff and parents were aware of this definition of vomiting. The incidence of vomiting was recorded in the PAR and DCSU by nursing staff and after discharge from the hospital by the parents.

The precise amount of anaesthetic drugs used and their associated administration tubing were recorded. The calculations used to determine variable costs of these drugs are in Appendix 1. *Variable costs*, were defined as those costs which change from patient to patient. *Fixed anaesthesia costs*, such as the cost of the anaesthetic machine, circuits and drug infusion devices, were not included in the cost calculations.

Sample size was predetermined by estimating an overall incidence of vomiting of 25% and that it would be clinically-important if one group had a 15% greater incidence of vomiting. The alpha error was set at 0.05 (two-sided) and Type II error was at 0.20. The projected sample size was 165 patients per group. Data were compared with one-way ANOVA, Chi-square analysis and linear regression analysis, whichever was most appropriate. Data are presented as mean $\pm$ SD.

Results

We enrolled 330 patients into the study. Sixteen patients in Group O were excluded because anaesthesia was induced with propofol. Also, a further 14 patients were excluded from the study and data analysis because the child was ASA physical class 3 (n=7), major protocol violations, such as the use of isoflurane for anaesthesia maintenance (n=4), and the parents' decision to opt out of the study (n=3). The groups were similar with respect to age, weight, sex, duration of surgery and number of muscles operated upon (Table I). Intraoperative IV fluid administration was 15 ± 8 ml·kg⁻¹. The distribution of potential confounding variables are described in Table I. The duration of stay in the PAR was slightly different between

the groups (Table I). Eighty-five patients did not receive acetaminophen while in hospital.

The groups had similar incidences of vomiting in the postoperative period (Table II). Premedication did not reduce vomiting, as 36% of the patients who received oral midazolam vomited. The 20 patients given neostigmine had a 20% incidence of vomiting, which was similar to the incidence of vomiting among the group that did not receive neostigmine. The 16 patients originally in Group O in whom an anaesthetic was induced with propofol had a similar incidence of vomiting as patients who had an inhalational induction (25% *vs* 27%). Each episode of in-hospital vomiting prolonged discharge by 17 ± 4 min, $P < 0.001$. All patients were discharged home from the DCSU on the day of surgery. The number of muscles operated upon influenced the incidence of vomiting (Table III).

Variable anaesthetic costs associated with the study ranged from \$2.57 CDN to \$60.39 CDN per patient and these costs were slightly greater in Group P (Table IV).

TABLE I Demographic data

Group	Ondansetron	Propofol
In	144	156
Age (yr)	6.1 $\pm$ 2.9	6.0 $\pm$ 3.0
Weight (kg)	23 $\pm$ 12	23 $\pm$ 12
# of muscles (n)		
1	51	52
2	83	92
3 or 4	10	12
Anaesthesia time (min)	54 $\pm$ 22	57 $\pm$ 23
PAR time (min)	43 $\pm$ 13	39 $\pm$ 12*
Premedication (n)	11	12
Mivacurium (n)	31	57
Vecuronium (n)	23	85
Neostigmine (n)	4	23
Antiemetic in-hospital (n)	9	4
Antiemetic at home (n)	2	1

Mean $\pm$ SD, PAR=post-anaesthetic recovery room,

* $P=0.002$ (Group O *vs* Group P).

TABLE II Incidence of vomiting

Group	Percent vomiting	Vomiting by location (%)			
		In-hospital		Out-of-hospital overall	
	overall	PAR	DCSU	Day 0	Day 1
O	27	2	9	14	12
P	26	1	10	18	8

O=ondansetron, P=propofol, PAR=post-anaesthetic recovery room, DCSU=day care surgical unit, Day 0 = Out-of-hospital on day of surgery, Day 1 = Day after surgery.

TABLE III Effect of number of muscles operated upon on vomiting

Number of muscles	n	Incidence of vomiting
1	111	21%*
2	183	27%
3 or 4	22	45%

* $P < 0.02$, 1 muscle *vs* 3 or 4 muscle

TABLE IV Anaesthetic costs per patient

Cost	Group O	Group P
Atropine	0.28 ± 0.16	0.29 ± 0.14
Propofol		12.38 ± 8.64
Infusion set	nil	3.95
Halothane	1.30 ± 0.76	nil
Neostigmine	0.03 ± 0.23	0.12 ± 0.38
Vecuronium	0.66 ± 1.85	2.68 ± 3.07
Mivacurium	0.56 ± 1.31	1.29 ± 2.07
Ondansetron	14.32 ± 6.52	nil
Total Cost	17.15 ± 8.10	20.71 ± 10.05*

* $P < 0.01$, Costs are in Canadian dollars.

Discussion

The current study shows that ondansetron and propofol have a similar effect on the incidence and frequency of vomiting by healthy children after strabismus surgery in an ambulatory care setting. The incidence of vomiting was similar to the 20–60% observed after a propofol-based anaesthetic^{8,9} and the 20–30% incidence noted after antiemetic prophylaxis with ondansetron.^{12,13} In concurrence with other investigators, vomiting after discharge from hospital appeared to be greater than in-hospital emesis.¹² This increased incidence may be due to a greater observation period, because post-discharge vomiting appeared to be of lesser clinical importance as only three patients received rescue antiemetics at home.

The incidence of in-hospital vomiting in the current study was almost minimal. None of the patients required unscheduled admission to hospital. Only 2% of the patients vomited in the PAR and 4% of the patients required a rescue antiemetic. With such a low incidence of in-hospital vomiting and low overall incidence of vomiting among the children undergoing one or two muscle procedures, the minimum stay in DCSU in our institution has been reduced to one hour after operation among those undergoing one or two muscle operations.

Numerous factors may alter the incidence of vomiting after strabismus surgery. Some, such as premed-

ication and surgical procedure, were controlled in the study protocol by stratification. Others, including anaesthetic technique, gastric aspiration, perioperative oral fluid ingestion and perioperative pain management were regulated by study design. However, some potential confounding factors were not as tightly managed. An example, in the current study, was the use of muscle relaxants. The requirement for muscle relaxants is different during intravenous anaesthesia from that with inhalation anaesthesia. Also, one of the clinical objectives was to minimize the cost of muscle relaxants and need for a reversal agent, neostigmine. Unfortunately, we do not know whether we achieved these objectives.

There is the potential for bias in this study. The attending anaesthetists, ophthalmologists and nurses in the PAR and DCSU were aware of the patient's treatment and could have altered their practice accordingly. To minimize this potential problem, each anaesthesia record was reviewed separately by two research assistants to confirm compliance with the study protocol. Post-operative surgical management and nursing practices were guided by the rigid guidelines of this protocol and these practices were followed by the research assistants. Bias also could have been introduced during the cointervention phase when a few patients received a rescue antiemetic.

Vomiting delayed discharge from hospital, but no patient required admission. Other factors which may alter discharge include discharge protocols, staff availability and patient sedation. Of note, sedation and vomiting were mild, so that we now discharge most of our patients one hour earlier than in the current study.

Within the current study, propofol-based anaesthesia was more expensive than halothane-based anaesthesia supplemented with ondansetron. Unfortunately, a complete economic analysis is not available in our health care system. Medical, nursing, allied health care and administration contribute directly and indirectly to health care costs. Anaesthetic drugs, which are usually a variable direct cost, are relatively easily evaluated, but are a minor component of total cost.¹⁴ The true cost of vomiting not only includes the cost of prophylactic drug administration, but also less tangible costs, such as those associated with a lost day at work, vomiting in a car, vomiting in a bed at home, nursing overtime, and lost day(s) at school are often far greater than drug costs. For the purpose of the current study, only drug costs directly attributed to the study and the cost of their specific administration set were assessed. Other anaesthetic costs, such as those attached to premedication, infusion pumps, syringes, drug waste and anaesthetic vaporizer were not tabulated. Drug use in the current study was minimized by

using multidose vials. Unfortunately, propofol cannot be safely stored in a multidose vial, so waste during a propofol-based anaesthetic is recognised, but its cost is unknown. Both methods of prophylaxis are expensive. It may be that less expensive alternatives with known efficacy, such as dimenhydrinate, may have superior cost-benefit ratios.¹⁵

In summary, two means of controlling vomiting with minimal adverse effects have been compared. The two methods of prophylaxis had similar antiemetic effects. In our local market, the anaesthetic technique in the ondansetron group was less expensive than that in the propofol group.

References

- 1 Abramowitz MD, Oh TH, Epstein BS, Ruttiman UE, Friendly DS. The antiemetic effect of droperidol following outpatient strabismus surgery in children. *Anesthesiology* 1983; 59: 579–83.
- 2 Patel RI, Hannallah RS. Anesthetic complications following pediatric ambulatory surgery: a 3-yr study. *Anesthesiology* 1988; 69: 1009–12.
- 3 Baines D. Postoperative nausea and vomiting in children. *Paediatr Anaesth* 1996; 6: 7–14.
- 4 Cunningham D, Turner A, Hawthorn J, Rosin RD. Ondansetron with and without dexamethasone to treat chemotherapy-induced emesis (Letter). *Lancet* 1989; i: 1323.
- 5 Carr AS, Splinter WM, Bevan J, Reid CR, Stephenson CA, Lerman J. Ondansetron reduces postoperative vomiting in pediatric strabismus surgery. *Anesthesiology* 1994; 81: A22.
- 6 Splinter WM, Baxter MRN, Gould HM, *et al.* Oral ondansetron decreases vomiting after tonsillectomy in children. *Can J Anaesth* 1995; 42: 277–80.
- 7 Snellen FT, Vanacker B, Van Aken H. Propofol-nitrous oxide *versus* thiopental sodium-isoflurane-nitrous oxide for strabismus surgery in children. *J Clin Anesth* 1993; 5: 37–41.
- 8 Weir PM, Munro HM, Reynolds PI, Lewis IH, Wilton NCT. Propofol infusion and the incidence of emesis in pediatric outpatient strabismus surgery. *Anesth Analg* 1993; 76: 760–4.
- 9 Tramèr M, Borgeat A, Rifat K. Postoperative nausea and vomiting after strabismus surgery in children – Effects of propofol, ondansetron and lidocaine. *Anesthesiology* 1993; 79: A1193.
- 10 Gan TJ, Ginsberg B, Grant AP, Glass PSA. Double-blind, randomized comparison of ondansetron and intraoperative propofol to prevent postoperative nausea and vomiting. *Anesthesiology* 1996; 85: 1036–42.
- 11 Splinter W, Noël L, Roberts D, Rhine E, Bonn G, Clarke W. Antiemetic prophylaxis for strabismus surgery. *Can J Ophthalmol* 1994; 29: 224–6.
- 12 Rose JB, Martin TM, Corddry DH, Zagnoev M, Kettrick RG. Ondansetron reduces the incidence and severity of poststrabismus repair vomiting in children. *Anesth Analg* 1994; 79: 486–9.
- 13 Davis A, Krige S, Moyes D. A double-blind randomized prospective study comparing ondansetron with droperidol in the prevention of emesis following strabismus surgery. *Anaesth Intensive Care* 1995; 23: 438–43.
- 14 Hawkes C, Miller D, Martineau R, Hull K, Hopkins H, Tierney M. Evaluation of cost minimization strategies of anaesthetic drugs in a tertiary care hospital. *Can J Anaesth* 1994; 41: 894–901.
- 15 Vener DF, Carr AS, Sikich N, Bissonnette B, Lerman J. Dimenhydrinate decreases vomiting after strabismus surgery in children. *Anesth Analg* 1996; 82: 728–31.
- 16 Morscher AH, Smith CE, Gordon GJ, Patel N. A simple spreadsheet tool for cost accounting anesthesia care (Letter). *Anesthesiology* 1994; 81: 514–6.

Appendix 1

Costs (Canadian Dollars)

Propofol - \$8.87 per 200 mg vial. Halothane - \$17.25 per 250 mL bottle. Ondansetron - \$4.30 per mg. Atropine - \$0.26 per 0.4 mg ampoule. Neostigmine - \$0.51 per 0.5 mg ampoule. Mivacurium - \$20.90 per 40 mg vial. Cost of halothane calculated using the formula described previously, where cost equals $(P \cdot F \cdot T \cdot M \cdot C) / 2412 \cdot d$, where P=inspired conc'n in %, F=fresh gas flow in L·min⁻¹, T = time in min, M=molecular weight (197.4 g), C=cost (\$0.069·mL⁻¹) and d=density (1.86 g·mL⁻¹)¹⁶.