

There Is No Dose-Escalation Response to Dexamethasone (0.0625–1.0 mg/kg) in Pediatric Tonsillectomy or Adenotonsillectomy Patients for Preventing Vomiting, Reducing Pain, Shortening Time to First Liquid Intake, or the Incidence of Voice Change

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BACKGROUND: Tonsillectomy is associated with postoperative nausea and vomiting (PONV) if no prophylaxis is administered. Previous studies have shown that a single dose of dexamethasone decreases the incidence of PONV. The most effective dose of dexamethasone to affect clinical outcome is yet to be defined.

METHODS: One-hundred-twenty-five children were enrolled in a double-blind, prospective, randomized, dose-escalating study of dexamethasone: 0.0625, 0.125, 0.25, 0.5, or 1 mg/kg, maximum dose 24 mg. Nonparametric ANOVA was used to analyze the incidence of vomiting by treatment group for 0 to ≤5 h, >5 to 24 h. The Cox Proportional Likelihood Ratio Test was used to compare the time of first vomit and time to first pain medication across treatment groups.

RESULTS: There was no difference in the incidence of vomiting for the five escalating doses of dexamethasone in the time period. There were no differences in secondary outcomes (analgesic requirements, time to first liquid, and change in voice) across treatment groups.

CONCLUSION: We conclude that the lowest dose of dexamethasone (0.0625 mg/kg) was as effective as the highest dose of dexamethasone (1.0 mg/kg) for preventing PONV or reducing the incidence of other secondary outcomes following tonsillectomy or adenotonsillectomy. There is no justification for the use of high-dose dexamethasone for the prevention of PONV in this cohort of children.

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Tonsillectomy and adenotonsillectomy in children are associated with a frequent incidence of postoperative nausea and vomiting (PONV) ranging from 50% to as high as 88% if no prophylaxis is administered (1,2). Previous studies have reported that administration of a single dose of dexamethasone has statistical and clinical impact in reducing the incidence of PONV, decreasing pain medication use, increasing oral intake, and decreasing airway swelling (3–6).

Dexamethasone has been administered to many children undergoing a variety of surgical procedures without major sequelae, although it is not a totally innocuous drug and may cause immune suppression and possibly delay in wound healing (7). Several dexamethasone dosages, either alone or in combination with other antiemetics, have been recommended in the pediatric tonsillectomy literature; however, these weight-adjusted doses vary nearly 20-fold (0.05 mg/kg to 1 mg/kg). (1,2,4,5,8–10) The maximum dose that has been recommended also varies between 8 mg and as high as 50 mg. (2,3,5,9,11) Although many studies have shown the effectiveness of a single dose of dexamethasone, the lowest effective dose to affect clinical outcome is yet to be clarified. A Cochrane analysis concluded that “further study is warranted to determine optimum dexamethasone dosing” (3). The purpose of our randomized, double-blind, dose-escalation study was to perform a preliminary study to determine a minimum effective dose of dexamethasone for decreasing the incidence of PONV after tonsillectomy or adenotonsillectomy in children as the primary end-point. Secondary end-points included: differences in the use of pain medications, decrease in

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time of first oral liquid intake, time to first soft food intake, and lesser airway swelling as demonstrated by a lower incidence of changes in the voice (5,11–16).

METHODS

The IRB approved this prospective, randomized, double-blind, dose-escalation study. The study was designed in consultation with the Biostatistical Research and Consulting group of Children's Memorial Research Center. A review of the available literature revealed conflicting results between high and low doses of dexamethasone in children; the lowest dose of dexamethasone used by itself as an antiemetic was 0.15 mg/kg whereas the highest dose was 1 mg/kg. At the time of this literature review, no lower doses as the sole antiemetic in children had been reported. Our prestudy power analysis used a study of 130 children who were randomized to receive a high dose of dexamethasone (1 mg/kg up to 25 mg) versus placebo and followed for 24 h. In that study, the incidence of vomiting was 48% in the treatment group compared with 88% in the placebo group (2). We assumed that the lowest dose in our study (0.0625 mg/kg) would likely be ineffective and similar to a placebo. Therefore, to have a power of 0.8 (two-tailed) and an α of 0.05, a minimum of 20 patients in each group would be required to demonstrate a difference between the lowest and the highest dexamethasone dose (Sample Power 2, SPSS, Chicago, IL). If there were a dose response then a much larger study (50 or more patients per group) would be required. The IRB asked that we perform an interim analysis at 25 patients per group; the statistician would determine the need for further study. Since there are a number of surgical approaches to this procedure that may affect swelling and postoperative pain responses (snare, cautery, microdebridement) the surgeons limited their approach to the one technique using electrocautery.

Children were randomized into treatment groups from a computer-generated randomization schedule such that the number of patients in each group would be equal. One-hundred-twenty-five patients were randomized to receive one of five escalating doses of dexamethasone: 0.0625 mg/kg, 0.125 mg/kg, 0.25 mg/kg, 0.5 mg/kg, or 1 mg/kg with a maximum dose of 24 mg. The randomized dexamethasone doses were diluted to an equal volume of 6 mL with normal saline so as to blind the drug dose given from the person administering the drug, the research nurse observer, as well as all other health care providers involved in the patient's care. A placebo control was not used, since the efficacy of dexamethasone has been demonstrated in numerous previous studies and confirmed by a Cochrane review (3,10,17–20). It was also not used because the surgeons would not have allowed patient participation since they considered dexamethasone administration a standard of care.

After obtaining written informed parental consent, we studied 125 children up to 8 yr of age, ASA

physical status I-II, and weight ≤ 24 kg undergoing tonsillectomy or adenotonsillectomy. Children over 24 kg, taking baseline antiemetics, having an abnormal airway, with a contraindication to dexamethasone, or receiving steroid-based medication were excluded. A history of motion sickness or previous incidence of PONV was noted.

Children were premedicated with oral midazolam (0.33 mg/kg) as indicated. A standardized anesthetic was used. All children had inhaled induction of anesthesia and maintenance with sevoflurane and nitrous oxide in oxygen. After an IV catheter was inserted, dexamethasone at a predetermined randomized dose, rocuronium 0.3–0.6 mg/kg and morphine 0.075 mg/kg were administered. All patients were tracheally intubated. Atropine (0.02 mg/kg IV) and neostigmine (0.05 mg/kg IV) were administered at appropriate times to antagonize neuromuscular blockade. At the conclusion of surgery, an orogastric tube was inserted under direct visualization by the surgeon, and gastric contents were suctioned. Patients were tracheally extubated in the operating room when fully awake.

Patients were then transported to the postanesthesia care unit (PACU), and observed at 5-min intervals for 50 min by our Anesthesia Research Nurse. The Objective Pain Scale¹ was used to evaluate the onset of pain. Pain rescue was provided with additional incremental morphine (0.05 mg/kg every 10 min) if the objective pain score was ≥ 6 for two consecutive 5-min intervals or if the patients articulated that their throat hurt. Patients were also observed for episodes of PONV; rescue was provided with ondansetron (0.1 mg/kg IV). The volume of lactated Ringer's solution administered was recorded from the time of IV insertion to PACU arrival, in the PACU, and in the 23-h (short stay) unit. Further episodes of vomiting, need for analgesia, time and volume of oral liquid and soft food intake were recorded on the patient record.

All ambulatory patients were observed for a minimum of 4–6 h postoperatively and were sent home when institutional criteria were met (21). Analgesia after discharge was provided with prescriptions of acetaminophen with codeine (120 mg/12 mg in 5 mL), with the codeine dose set at 1 mg/kg to a maximum of 30 mg. All patients were also sent home with oral antibiotics: amoxicillin, azithromycin, or clindamycin. Parents were given a patient care diary to record the time and number of further episodes of vomiting, time and dose of analgesics, time to soft food intake, and time to hard food intake.

Parents received a 24 h postanesthesia phone call to review the patient care diary of vomiting, the time of these events, the amount of pain medication administered and the time of administration, signs of changes

¹Broadman LM, Rice LJ, Hannallah RS. Testing the validity of an Objective Pain Scale for infants and children. *Anesthesiology* 1988;69:A770.

in his/her voice (Mickey Mouse voice, rhinolalia aperta) (12), time of oral intake of soft foods and solids.

Statistical Analysis

As required by the IRB, the randomization code was broken at 25 patients per group and an analysis was performed. Since there were no differences in incidence of any of the outcome variables when comparing the highest and lowest dose and since the outcomes for the doses in between provided no further suggestion of a dose effect, we terminated patient enrollment at the IRB's request. Data were summarized using frequencies for categorical variables and means and standard deviations for continuous variables. Frequencies and means of demographic data were compared across randomized treatment groups using χ^2 test and Analysis of Variance (ANOVA), respectively under the intent-to-treat model.

The incidence of PONV over the 24 h follow-up was compared among treatment groups using a χ^2 test. Incidence of PONV from 0 to 5 h, from >5 h to 24 h, and 0 to 24 h was also compared using a χ^2 test. The median number of vomiting episodes per person was compared among treatment groups using a nonparametric ANOVA (Kruskal-Wallis). Logistic regression modeling was used to compare the incidence of PONV with total anesthesia time including anesthesia time longer than and <30 min and age <3 yr compared with children ≥ 3 yr. Vocal change at home among treatment groups was also compared using a χ^2 test.

The Cox Proportional Hazard Model was used to compare the time to first vomiting, time to first analgesic medication, and time to first liquid intake among treatment groups using a time-to-event approach. Patients who were lost to follow-up once released from the hospital were censored at the time of their discharge from the hospital.

The number of times pain medication was given (pain rescue) was compared across treatment groups using the Kruskal-Wallis test. Pain and sedation scores were compared at 10 time points using ANOVA. The Spearman correlation was used to examine the association among the number of vomiting episodes and the number of pain rescues.

All analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, NC) and S-Plus version 7.0 (Insightful Corporation, Seattle, WA). Conclusions were made at 0.05 level of significance.

RESULTS

One-hundred-twenty-five patients, all of whom underwent electrocautery tonsillectomy, were enrolled in this study. There were nine protocol violations: one patient received ondansetron in the absence of vomiting; one patient required return to the operating room for bleeding and thus was anesthetized a second time; two patients had myringotomy and tube insertion added to the procedure after enrollment; four

patients had injection of local anesthetic by the surgeon into the tonsillar bed; and one patient received a second dose of dexamethasone at 1185 min. Of these nine patients, we excluded four from the final analysis: those that had undergone myringotomy and tube placement, the one who received ondansetron in the absence of vomiting, and the patient who had to return to the operating room for bleeding. We included the other patients since the primary outcome variable, vomiting, was unlikely to be affected by the injection of local anesthetic. The data for the patient who received a second dose of dexamethasone were included only up until the time of the second dose. Complete data were collected for 108 patients; the parents of 13 patients were unreachable by phone. Final analysis included 121 patients with modifications made according to the time of last follow-up.

There was no significant difference among treatment groups for gender distribution, age, weight, anesthesia time, total IV fluid, type of antibiotic, or number lost to follow-up (Table 1). There was no difference in the incidence of vomiting among treatment groups for the 24 h follow-up period ($P = 0.50$). Also, there was no significant difference among treatment groups for the first 5 h ($P = 0.10$), or from 5 to 24 h ($P = 0.35$) (Table 2). There was no significant difference among treatment groups in time to first vomiting episode ($P = 0.28$) (Fig. 1). There was no significant difference in the rate of PONV overall for children whose anesthesia lasted longer than 30 min compared with those whose anesthesia was <30 min (40.0% vs 46.6%, $P = 0.90$). There was no significant difference overall in the incidence of PONV in children who were <3 yr compared with those ≥ 3 years (48% vs 46%, $P = 0.90$). Fifty-eight of the 108 patients for whom we had complete data had no PONV at all.

There were no differences in secondary outcomes across treatment groups. The incidence of vocal changes, characterized by a "Mickey Mouse" pitched voice, was not different among treatment groups (Table 2, $P = 0.22$). The number of pain rescues was evenly distributed across the treatment groups during the three time intervals of 0–50 min ($P = 0.52$), 51 min to 5 h ($P = 0.82$), and >5 to 24 h ($P = 0.78$). There was no difference in pain scores or sedation scores measured at each of 10 time points. The P values ranged from 0.12 for the largest difference to 0.88 for the smallest difference. There was no difference among treatment groups in time to first pain rescue (Fig. 2) ($P = 0.88$). There was no association among vomiting episodes and the need for pain medications ($P = 0.28$ – 0.49). Time to first liquid intake was not significantly different among treatment groups (Table 2) ($P = 0.30$). A history of motion sickness has been correlated with an increased risk for PONV (19). Although we collected these data, there was insufficient power to comment on how this history may have contributed to the incidence of PONV.

Table 1. Demographic and Clinical Data

	Randomized to dexamethasone dose level (mg/kg)						P-value
	Total N = 121	0.0625 N = 24	0.125 N = 25	0.25 N = 23	0.5 N = 25	1.0 N = 24	
Gender—number of patients:							
Males	73	14	14	12	15	18	0.55
Females	48	10	11	11	10	6	
Age (yr) mean (\pm SD)	4.3 (1.4)	4.0 (1.1)	4.2 (1.4)	4.8 (1.8)	4.5 (1.4)	4.1 (1.4)	0.39
Age range (yr) minimum to maximum		2.15–6.02	2.19–7.16	1.86–8.87	2.12–7.22	2.02–7.78	
Percent >3 yr of age	82	71	84	83	92	79	
Weight (kg) mean (\pm SD)	17.5 (3.6)	16 (3)	17 (4)	19 (3)	18 (3)	17 (4)	0.20
Weight range (kg) minimum to maximum		10.60–22.60	11.50–23.70	12.80–24.00	11.80–23.00	10.90–24.00	
Lost to follow-up	13	5	0	3	2	3	0.18
Antibiotic treatment (N)							
Amoxicillin	112	20	23	22	25	22	0.40
Azithromycin	8	3	2	1	0	2	
Clindamycin	1	1	0	0	0	0	
Total IV fluid mean (\pm SD)	290 (90)	284 (97)	278 (80)	293 (98)	299 (94)	294 (83)	0.92
Anesthesia time (min) mean (\pm SD)	42.0 (8.8)	42.9 (9)	40.9 (10)	44.7 (9)	41.9 (6)	39.5 (9)	0.31

Table 2. Vomiting Incidence (Yes) or Not at All (No)

Treatment group	Did child vomit Y/N within first 5 h?	Did child vomit between >5 to 24 h?	Did child vomit at any time within 24 h (Overall)?	Vocal changes at home Y/N	Mean hours to first liquid intake \pm SD (Median)
Frequency/Total Pct (95% CI)	N = 121	N = 108*	N = 108*	N = 108*	N = 121
0.0625 mg/kg	9/24 37.5% (18.8, 59.4)	7/19 36.8% (16.3, 61.6)	9/19 47.4% (24.5, 71.1)	4/19 21% (6.1, 45.6)	N = 24 1.13 \pm 0.79 (0.90)
0.125 mg/kg	9/25 36.0% (18.0, 57.5)	6/25 24.0% (9.4, 45.1)	11/25 44.0% (24.4, 65.1)	11/25 44% (24.4, 65.1)	N = 25 1.32 \pm 1.73 (0.80)
0.25 mg/kg	9/23 39.1% (19.7, 61.5)	7/20 35.0% (15.4, 59.2)	9/20 45.0% (23.1, 68.5)	9/20 45% (23.1, 68.5)	N = 23 1.19 \pm 0.77 (0.90)
0.5 mg/kg	5/25 20.0% (6.8, 40.7)	7/23 30.4% (13.2, 52.9)	8/23 34.8% (16.4, 57.3)	11/23 47.8% (26.8, 69.4)	N = 25 1.90 \pm 1.66 (1.50)
1.0 mg/kg	14/24 58.3% (36.6, 77.9)	11/21 52.4% (29.8, 74.3)	13/21 61.9% (38.4, 81.9)	12/21 57.1% (34.0, 78.2)	N = 24 1.69 \pm 1.93 (0.90)
Total	46/121 38.0% (29.4, 47.3)	38/108 35.2% (26.2, 50.0)	50/108 46.3% (36.7, 56.2)	47/108 43.5% (34.0, 53.4)	

* Includes only the patients with complete 24-h follow-up.

χ^2 test $P = 0.10$ – 0.50 . Treatment group was not associated with likelihood of vomiting one or more times within the first 5 h or for >5 to 24 h or for within 24 h. No significant difference was found among the treatment groups for vocal changes ($\chi^2 P = 0.22$). No observations were censored for time to first liquid intake because every patient took liquids within 9 h; data were missing for four patients. No significant difference was found between treatment groups, $P = 0.30$ (Cox Proportional Hazard Likelihood Ratio Test).

DISCUSSION

PONV after tonsillectomy is a common adverse outcome that may lead to dehydration and conversion from outpatient basis to unplanned hospital admission (21). Single IV doses of dexamethasone have been shown to significantly reduce the incidence of PONV in pediatric tonsillectomy patients; however published doses range from 0.15 to 1.0 mg/kg with maximum doses of up to 50 mg (1,4–6,11,22). Lower doses have proven effective when

combined with other antiemetics, so called “multi-modal therapy” (9,23–25). Many studies included children who exceeded the weight in kilograms over the maximum dose allowed, i.e., there was no weight-normalization of treatment groups (2,3,5,6,9). In addition, some studies using 1 mg/kg of dexamethasone reported higher vomiting rates (30%–48%) (2,26) than those reported with lower doses (5%–40% for 0.5 mg/kg and 4% with 0.15 mg/kg) (1,8,22,27,28). Thus the literature is confusing and contradictory regarding

Figure 1. Time-to-event analysis for first vomiting episode was performed; tick marks indicate time of censoring for patients who did not have complete follow-up ($n = 13$). No significant difference was found among dose levels, $P = 0.28$ (Cox Proportional Hazard Likelihood Ratio Test).

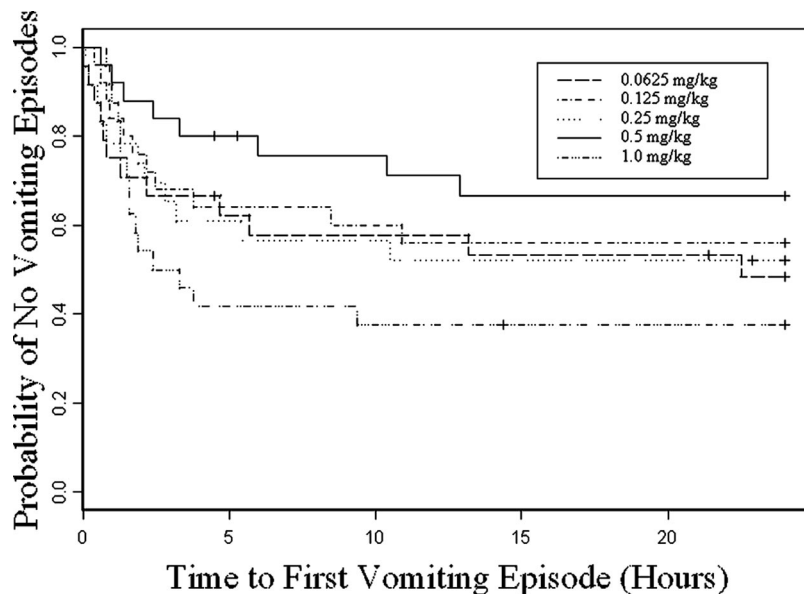
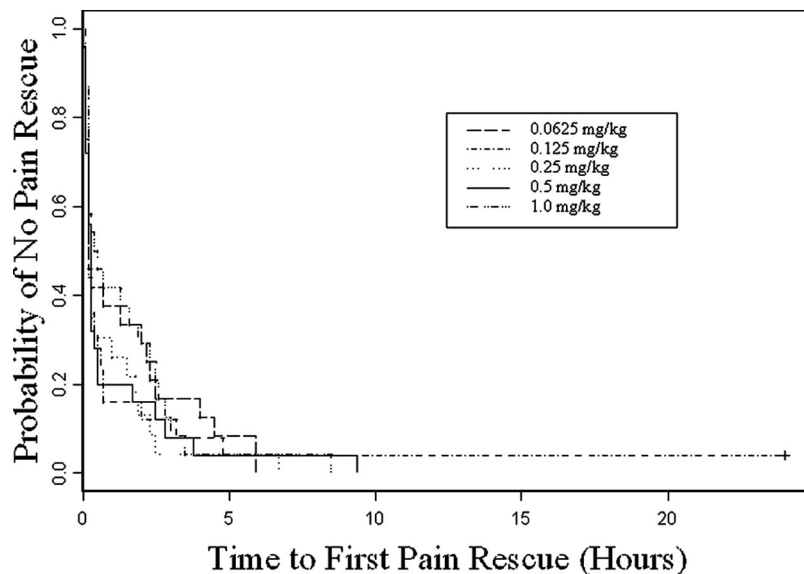


Figure 2. Time-to-event analysis for first analgesic was performed; tick marks indicate time of censoring for patients who did not have complete follow up to the time of first analgesic administration ($n = 2$). No significant difference was found among dose levels, $P = 0.88$ (Cox Proportional Hazard Likelihood Ratio Test).



the rates of emesis and the doses of dexamethasone that are effective in children. In addition, each study collected information regarding vomiting for varying periods of time after completion of surgery, and most did not standardize surgical technique or postoperative analgesia management.

To best explore whether there was a hint of a dose response to dexamethasone for the prevention of PONV in this pediatric population, as well as for a reduction in other markers of improved outcomes—reported to follow administration of dexamethasone to a tonsillectomy population, we strictly dose/weight-normalized our children, and we administered ondansetron only as a rescue antiemetic. We did not have a placebo group, since the literature is clear concerning the benefits of single-dose dexamethasone in terms of reducing the incidence of vomiting (3,10,17–20). In addition, it is our standard practice to administer dexamethasone to all patients undergoing a tonsillectomy or adenotonsillectomy. Since the literature is so

contradictory, we powered the size of our study on the basis of a study that examined the highest dose of dexamethasone (1 mg/kg) and compared it with what we considered to be a very low dose (0.0625 mg/kg), which was approximately 40% of the lowest reported effective dose of dexamethasone shown to be effective for preventing PONV in children after adenotonsillectomy (8). Our reasoning was that our surgeons wanted all patients to receive dexamethasone, we did not know the lowest effective dose, and we assumed that this low dose would actually be equivalent to a placebo. Our study found that the lowest dose of dexamethasone (0.0625 mg/kg) just as effective in preventing vomiting as the highest dose (1 mg/kg). This same low dose was also not significantly different in effectiveness for all secondary measures: time to first liquid, change in voice, time to first pain rescue, number of pain rescues. In fact, the incidence of some of these secondary outcomes (vomiting, mean time to first vomiting, percentage of patients with a change in

voice consistent with swelling [Mickey Mouse voice, rhinolalia aperta], and mean time to first pain medication), was longer in the group who had received the highest dose of dexamethasone (1 mg/kg). Another way of examining these data would be to assume that all patients who were lost to follow up, in fact, vomited during the first 24 postoperative hours. This would be the worst-case scenario regarding these patients but even with this assumption the conclusions would not change, since this would then result in 14 of 25 patients in the lowest dose group having vomiting at any point during the first 24 postoperative hours and 16 of 25 in the highest dose group. A study with sufficient power to show a difference among these rates of vomiting would require 590 patients in each group, and the results would show that there was less vomiting with the lower dose of dexamethasone, i.e., the reverse of what would be expected. Likewise, if we compare the incidence of voice change as an indicator of postoperative swelling, the raw incidence was 21% for the lowest dose and 57% for the highest dose of dexamethasone. If we again take the worst case scenario and assume that all patients for whom these data were not available, in fact, had voice changes, then the incidence would be 40% in the lowest dose group and 64% in the patients who received the highest dose; this is also the reverse of what would be expected if dexamethasone contributes to reduced swelling.

A Cochrane analysis of medications to prevent PONV (primarily adult literature) suggested that the "risks for most outcomes were greater after smaller doses of dexamethasone" and that this risk was "greater with half the dose" (29). This study did not find a relationship between the type of surgery and risk for emesis. Another study of adult females undergoing gynecologic procedures compared placebo with 1.25, 2.5, 5.0, or 10 mg of dexamethasone; with weight normalization, this was approximately equivalent to 0.021, 0.044, 0.91, and 0.172 mg/kg (30). The incidence of emesis was significantly less for the three higher dexamethasone doses compared with placebo and dose of 1.25 mg, suggesting that our study may not have reached the low end of the dose-response curve; but unlike the Cochrane review, ours found no suggestion of a dose response, despite a 16-fold variation in a weight-adjusted dose of dexamethasone. Another pediatric study also failed to find that tonsillectomy was associated with a higher risk for vomiting, but suggested that age ≥ 3 yr and duration of surgery of ≥ 30 min were positively associated with vomiting; we were unable to find such a relationship (31). Our results illustrate why a placebo-controlled trial and a lower dose range would have provided additional information in defining the lesser end of the dose-response curve.

Although vomiting is considered a surrogate outcome marker, we specifically chose to collect only data that could be accurately quantitated (vomiting, time to

first vomiting event, time to first liquid intake, time to first pain medication, and change in voice). We felt that it would be highly impractical to attempt to collect data regarding nausea since small children are unable to verbalize this feeling to their parents. Likewise, satisfaction is very difficult to quantify, since young children are unable to verbalize or even understand what this means and the parents have no basis for comparison.

Overall, the incidence of any vomiting in this entire cohort was quite high (46%) but our incidence is virtually identical to that reported by Splinter and Roberts (8) who used the lowest effective dose (0.15 mg/kg, vomiting rate 40%) and to Pappas et al. (2) who studied the highest effective dose (1 mg/kg, vomiting rate 48%). Our findings are also consistent with another study that looked at the minimum effective dose of dexamethasone (50, 100, 150 μ g/kg) for the prevention of vomiting after tonsillectomy. In that study, there was no significant difference among treatment groups; however, since all the children also received ondansetron (50 μ g/kg) it is unclear if the antiemetic effect observed was related to the dexamethasone, to the ondansetron, or to the combined effects (9). In fact the placebo group in this study was not different from any of the other groups, which leads to further confusion regarding the efficacy of dexamethasone. The results of that study are inconsistent with many others in the literature and to the Cochrane reviews. Another recent study (32) examining PONV in children undergoing strabismus surgery found results similar to ours; there was no advantage in 1 mg/kg, 0.5 mg/kg or 0.25 mg/kg; however even the low dose (0.25 mg/kg) was more effective than saline. That study also examined blood glucose values in the PACU and found no difference in blood glucose values between the saline control group and the three dexamethasone treated groups.

On the basis of our findings, there were no significant differences among any dexamethasone doses, and particularly between the lowest dose (0.0625 mg/kg) to highest dose (1 mg/kg), for the incidence of vomiting, pain scores, time of oral intake, and voice changes (rhinolalia aperta). Although the number of patients in each group was relatively small, there was no hint of a dose response. Thus this exploratory study, as well as studies in adults, suggest that perhaps even a smaller dose of dexamethasone might be effective. On the basis of this study, it is our recommendation to use the lowest dosage of dexamethasone 0.0625 mg/kg to prevent vomiting in pediatric patients undergoing tonsillectomy. There would appear to be no justification for the use of higher doses of dexamethasone in this cohort of patients.

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