

Dexamethasone and Risk of Nausea and Vomiting and Postoperative Bleeding After Tonsillectomy in Children

A Randomized Trial

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TONSILLECTOMY IS ONE OF THE most frequently performed surgical procedures in children. In 1998, the rate varied from 19 per 10 000 children in Canada to 118 per 10 000 in Northern Ireland.¹ In the United States, about 186 000 procedures are performed on an outpatient basis every year.² Common complications of tonsillectomy are postoperative nausea and vomiting (PONV), pain, and bleeding.³ Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used in this setting for their pronounced analgesic efficacy and a lack of the emetogenic effect inherent to opioids. However, classic NSAIDs, through reversible platelet inhibition, further increase the risk of bleeding after tonsillectomy.^{4,5}

Dexamethasone has antiemetic properties in the surgical setting.⁶ An international expert panel recommended dexamethasone, alone or as part of a multimodal regimen, for

Context Dexamethasone is widely used to prevent postoperative nausea and vomiting (PONV) in pediatric tonsillectomy.

Objective To assess whether dexamethasone dose-dependently reduces the risk of PONV at 24 hours after tonsillectomy.

Design, Setting, and Patients Randomized placebo-controlled trial conducted among 215 children undergoing elective tonsillectomy at a major public teaching hospital in Switzerland from February 2005 to December 2007.

Interventions Children were randomly assigned to receive dexamethasone (0.05, 0.15, or 0.5 mg/kg) or placebo intravenously after induction of anesthesia. Acetaminophen-codeine and ibuprofen were given as postoperative analgesia. Follow-up continued until the 10th postoperative day.

Main Outcome Measures The primary end point was prevention of PONV at 24 hours; secondary end points were decrease in the need for ibuprofen at 24 hours and evaluation of adverse effects.

Results At 24 hours, 24 of 54 participants who received placebo (44%; 95% confidence interval [CI], 31%-59%) had experienced PONV compared with 20 of 53 (38%; 95% CI, 25%-52%), 13 of 54 (24%; 95% CI, 13%-38%), and 6 of 52 (12%; 95% CI, 4%-23%) who received dexamethasone at 0.05, 0.15, and 0.5 mg/kg, respectively ($P<.001$ for linear trend). Children who received dexamethasone received significantly less ibuprofen. There were 26 postoperative bleeding episodes in 22 children. Two of 53 (4%; 95% CI, 0.5%-13%) children who received placebo had bleeding compared with 6 of 53 (11%; 95% CI, 4%-23%), 2 of 51 (4%; 95% CI, 0.5%-13%), and 12 of 50 (24%; 95% CI, 13%-38%) who received dexamethasone at 0.05, 0.15, and 0.5 mg/kg, respectively ($P=.003$). Dexamethasone, 0.5 mg/kg, was associated with the highest bleeding risk (adjusted relative risk, 6.80; 95% CI, 1.77-16.5). Eight children had to undergo emergency reoperation because of bleeding, all of whom had received dexamethasone. The trial was stopped early for safety reasons.

Conclusion In this study of children undergoing tonsillectomy, dexamethasone decreased the risk of PONV dose dependently but was associated with an increased risk of postoperative bleeding.

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PONV prophylaxis in adults and children.⁷ It has been suggested that, especially in children undergoing tonsillectomy, dexamethasone is useful, not only for its antiemetic but also for its analgesic effects, and that it should be used routinely because the adverse effects and cost appear negligible.⁸⁻¹¹ Indeed, dexamethasone for tonsillectomy has become standard care in many institutions.¹²

The dose response of dexamethasone for prevention of PONV symptoms in pediatric tonsillectomy remains unclear, although doses up to 1 mg/kg have been tested.¹³⁻¹⁶ Also, the adverse effect profile has not yet been established. Finally, if dexamethasone were indeed analgesic in this setting, fewer postoperative analgesics such as NSAIDs would be needed postoperatively and, theoretically, patients would be less at risk of postoperative bleeding. We set out to address these issues in a randomized, placebo-controlled, dose-finding study. That trial had to be stopped prematurely for safety reasons.

METHODS

Study Population, Intervention, and Protocol

We recruited study participants from the University Hospital of Geneva, Switzerland. This is the only public hospital in Geneva (population, 450 000). Children aged 2 to 17 years scheduled for elective adenotonsillectomy for recurrent tonsillitis or sleep apnea were eligible to enter the study. Children were excluded if they had a history of allergy or hypersensitivity to dexamethasone, recent (<1 month) therapy with steroids or immunotherapy, mental retardation, if they had taken antiemetic medication within 24 hours before surgery, or if they had diabetes, recent vaccination (<1 month), or varicella infection (<1 month).

In accordance with published recommendations,¹⁷ and because for surgical patients without liver dysfunction or history of oral anticoagulant use routine testing has no benefit in assessment of bleeding risk,¹⁸ no routine pre-

operative blood tests for bleeding disorders were performed. However, children in whom a hemostasis disorder was suspected through patient or family history or those who were taking aspirin, classic NSAIDs, or other drugs that were interfering with coagulation were not considered for inclusion in the study.

The study was approved by the institutional ethics committee and the Swiss agency for therapeutic products (Swissmedic). Written informed consent was obtained from parents and also from children if they were able to read and sign a specifically designed information sheet.

Procedures

Children were randomly assigned to 1 of 4 groups: dexamethasone 0.05, 0.15, or 0.5 mg/kg, or placebo (physiological saline). Randomization was done in blocks of 40 children (10 per group). Study medications were produced and randomized (using colored balls) by the pharmacy of Geneva University Hospital as indistinguishable 20-mL syringes and were injected intravenously on a milliliters-per-kilogram body weight basis (maximum dose of dexamethasone, 20 mg) after induction of anesthesia.

Children received oral midazolam, 0.3 mg/kg (maximum dose, 10 mg), as a premedication. Anesthesia was induced with sevoflurane or propofol and was maintained using a volatile anesthetic. Alfentanil was used for intraoperative analgesia. According to the anesthesiologist's preference, the trachea was intubated with or without a nondepolarizing neuromuscular blocking drug. During surgery, children received rectal acetaminophen, 40 mg/kg (maximum dose, 750 mg), and 20 to 25 mL/kg of a balanced salt solution with 1% glucose. In case of residual paralysis, reversal was with intravenous neostigmine, 0.05 mg/kg, and glycopyrrolate.

For tonsillectomy, 2 to 4 mL of bupivacaine 0.25% with epinephrine 1:200 000 was infiltrated around the tonsils. Classic complete tonsillectomy

with dissection in the pericapsular plane was performed in all children. One of 3 surgical techniques was used according to the surgeon's preference: a cold technique (dissection with cold steel instruments, hemostasis with gauze compression), a hot technique (dissection and hemostasis with electric bipolar forceps),¹⁹ or a combination of both. No packings were used.

After surgery, children were transferred to the postanesthesia care unit and 2 hours later to the ward, where they stayed overnight. In the postanesthesia care unit, children received intravenous boluses of morphine, 0.03 mg/kg, as analgesia. On the ward, analgesia was with oral or rectal acetaminophen-codeine (maximum daily dose of acetaminophen, 50 mg/kg). When pain relief was considered inadequate (see below), ibuprofen was added (maximum daily dose, 30 mg/kg). Children were free to eat and drink as soon as the surgeon confirmed through visual examination the absence of bleeding from the tonsillar bed. Children were discharged home the day after surgery. Analgesia at home was identical as on the ward.

End Points and Definitions

The primary objective was to investigate the dose-effect relationship of dexamethasone for the prevention of PONV at 24 hours. Vomiting was the forcible ejection of contents of stomach through the mouth. Retching (ie, the unproductive effort to vomit) was considered vomiting. Nausea was recorded if the child was able to express it. Rescue medication for PONV was with intravenous ondansetron, 50 µg/kg.

The secondary objective was to investigate the potential analgesic efficacy of dexamethasone. Pain intensity was recorded using 1 of 3 pain scales according to age and comprehension of the child: a 0- to 10-point visual analog scale (VAS), the 0- to 10-point revised Faces Pain Scale (rFP),²⁰ or the 4- to 13-point Children of Eastern Ontario Pain Scale (CHEOPS).²¹ A VAS or rFP score of less than 3 and a CHEOPS score of less than 8 were regarded as ad-

equate pain relief. The number of children needing morphine in the postanesthesia care unit and those needing ibuprofen during the first 24 hours were recorded.

Other outcomes included capillary serum glucose level after induction and at the end of surgery, delay until the first oral intake, and, using a 0- to 10-point scale, the child's quality of sleep and the nurses' and parents' overall satisfaction.

Bleeding episodes were separated into 3 categories: category 1, a history of bleeding leading to readmission but without evidence of bleeding at medical examination; category 2, readmission due to bleeding with evidence of bleeding at medical examination but no need for reoperation; and category 3, emergency reoperation due to bleeding.

In the postanesthesia care unit and on the ward until discharge at 24 hours, recordings were made by nurses. Parents were given a questionnaire to be filled in daily after discharge and were

asked to bring it back to the routine surgical follow-up, which was scheduled for all children after 10 days. However, parents were instructed to come back to the otolaryngology outpatient clinic or to the emergency department in case of serious adverse events. They received oral and written instructions to provide an exclusively cold or room-temperature soft diet.

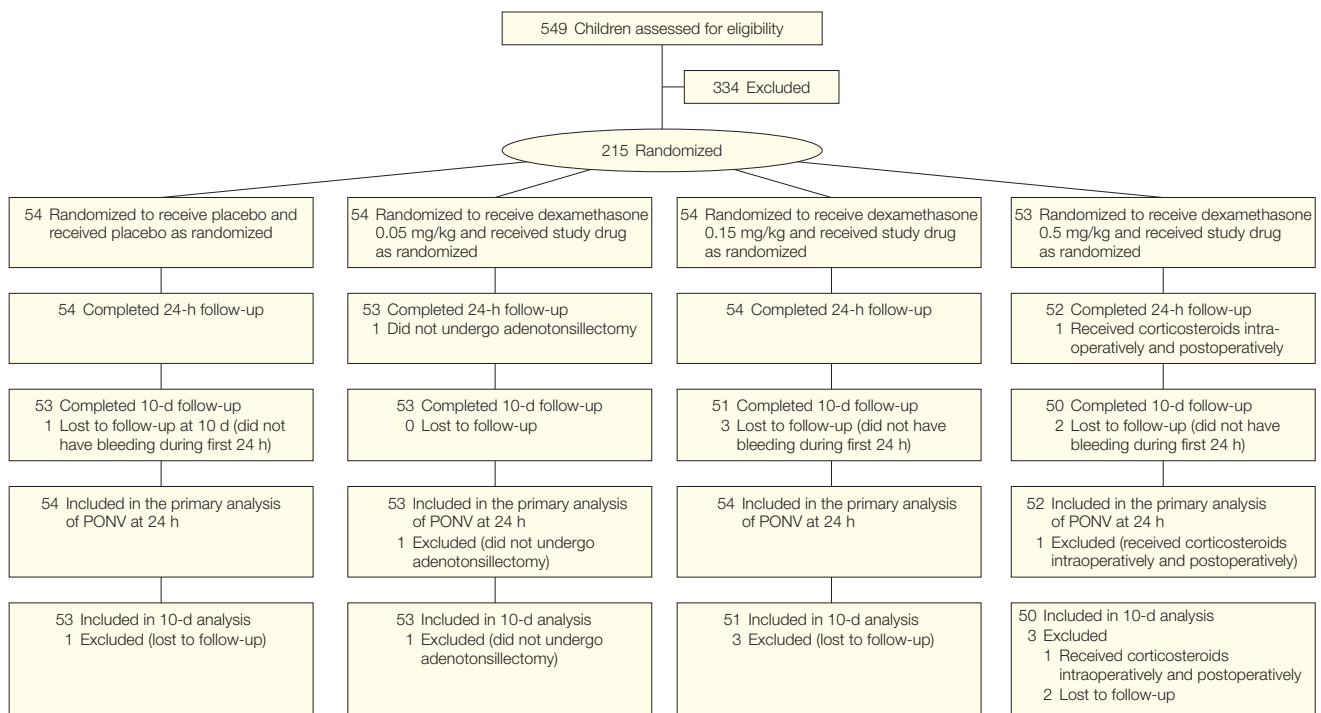
Early Termination of the Trial

The randomization code was broken after 200 children to allow for an interim analysis. This unplanned analysis was triggered by a surprisingly high number of postoperative bleeding episodes in study participants and the decision of the university hospital to transfer these interventions from the division of Otolaryngology–Head and Neck Surgery to the children's hospital. The unexpected management decision was likely to threaten the successful termination of the study. There was an intention to continue enrollment, had the primary end point (significant dose re-

sponse for PONV; $P < .005$) not been achieved at this time point. For that reason, only 2 of us (N.E. and M.R.T.) were given access to the randomization code; all other investigators remained unaware of group assignment. This interim analysis revealed a statistically significant and dose-dependent antiemetic effect of dexamethasone at 24 hours. However, the analysis also revealed a significant increase in the number of hemorrhages in children who had received dexamethasone.

After having consulted the institutional ethics committee, we stopped the trial prematurely. This shared decision was driven by 4 issues. First, study participants were children. Second, posttonsillectomy hemorrhage is a potential major harm. Third, at the time point of the interim analysis, the main end point of the study was already well documented. And fourth, in this context, dexamethasone could not be regarded as a vital treatment and without alternative. When the trial was stopped, 215 children had

Figure 1. Participant Flow



PONV indicates postoperative nausea and vomiting.

been randomized. To ensure that all bleeding episodes had been identified (ie, including those that happened after the 10-day follow-up), 2 surgeons (B.N.L. and R.G.), who were still unaware of study group assignment, reviewed the medical records of all randomized children to look for any emergency admission after the 10-day follow-up.

Statistical Analyses

We expected a cumulative 24-hour PONV incidence of 50%. A reduction to 25% was regarded as a relevant improvement in this context.²² Seventy children were required in each group for 80% power to detect such a reduction with a significance level of .05. We intended to randomize 80 children in each group to allow for dropouts. A post hoc power analysis revealed that with 50 children per group (ie, at the time of the interim analysis), the power to study the antiemetic efficacy of dexamethasone was 67%.

Baseline characteristics were compared using the Mann-Whitney or Pearson χ^2 test as required. Dexameth-

asone groups were individually compared with the placebo group. A 2-sided $P < .05$ was considered statistically significant.

The crude associations between dexamethasone groups and outcomes were analyzed using simple univariate analyses. Variables identified as potential confounding factors in previous studies were then introduced into a bivariate logistic regression model including dexamethasone exposure, outcome, and the potentially confounding factor. Crude and adjusted estimates were compared to assess the degree of confounding; variables were considered confounders if the estimates differed by more than 10%. A multivariate logistic regression model was then built that included all potential confounding factors. If the exclusion of a variable from the model did not decrease its fit to the data (assessed by a likelihood ratio test comparing a model including the variable with the nested model excluding it; $P > .10$) and increased its goodness of fit (assessed by a higher P value of the Hosmer-Lemeshow test grouped on 10 quan-

tiles), the variable was excluded from the multivariate model. Odds ratios were converted to relative risks. Collinearity was assessed by comparing the standard errors from the crude and the adjusted models. Interactions between exposure and potential confounders were not systematically assessed because of a lack of a priori hypotheses.

Departure from linear trend was assessed using the likelihood ratio test comparing logistic regression models considering dexamethasone doses as categorical or continuous variables. A linear relationship was assumed if $P > .10$. If the P value of the Wald test on the logistic regression coefficient was $< .05$, the dose-response relationship was considered significant.

Kaplan-Meier curves were built to illustrate the time to the first bleeding episode for each group separately; groups were compared using the log-rank test. Analyses at 24 hours were performed on an intention-to-treat basis; impact of losses to follow-up was assessed in sensitivity analyses. Analyses were performed using Stata, ver-

Table 1. Baseline Characteristics of the Study Population^a

Characteristics	Placebo (n = 54)	Dexamethasone, 0.05 mg/kg (n = 53)	Dexamethasone, 0.15 mg/kg (n = 54)	Dexamethasone, 0.5 mg/kg (n = 52)
Age, median (range), y	6 (3-11)	6 (2-13)	5 (3-12)	6 (2-16)
Body mass index, median (range) ^b	15.8 (13.1-27.6)	16.0 (11.8-24.0)	15.6 (11.7-24.2)	15.0 (12.5-37.3)
Male	28 (51.9)	26 (49.1)	29 (53.7)	29 (55.8)
Indication for surgery				
Obstructive sleep apnea	35 (64.8)	36 (67.9)	36 (66.7)	30 (57.7)
Recurrent tonsillitis	12 (22.2)	4 (7.5)	9 (16.7)	13 (25.0)
Both	7 (13.0)	13 (24.6)	9 (16.7)	9 (17.3)
Anesthesia				
Induction with sevoflurane	41 (75.9)	43 (81.1)	41 (75.9)	39 (75.0)
Induction with propofol	13 (24.1)	10 (18.9)	13 (24.1)	13 (25.0)
Use of nitrous oxide	43 (80.0)	31 (58.5) ^c	36 (67.0)	36 (69.2)
Use of neostigmine	2 (3.7)	2 (3.8)	3 (5.6)	3 (5.8)
Surgery				
Tonsillectomy only	3 (5.6)	4 (7.6)	5 (9.3)	7 (13.5)
Adenotonsillectomy	51 (94.4)	49 (92.5)	49 (90.7)	45 (86.5)
Cold technique	4 (7.4)	1 (1.9)	5 (9.3)	3 (5.8)
Hot technique	24 (44.4)	18 (33.9)	19 (35.2)	25 (48.1)
Combined cold and hot techniques	26 (48.2)	34 (64.2)	30 (55.6)	24 (46.2)

^aData are expressed as No. (%) of participants unless otherwise indicated. There were no significant differences in baseline characteristics between study groups except as noted below.

^bBody mass index was calculated as weight in kilograms divided by height in meters squared.

^c $P < .05$ by Pearson χ^2 comparing dexamethasone, 0.05 mg/kg, vs placebo.

sion 9 (Stata Corp, College Station, Texas), and Microsoft Excel, version 11.3 (Microsoft Inc, Redmond, Washington).

RESULTS

Patients and Enrollment

Between February 2005 and December 2007, 215 children were randomly assigned to receive placebo (n=54) or dexamethasone, 0.05 (n=54), 0.15 (n=54), or 0.5 (n=53) mg/kg (FIGURE 1). All received their assigned study treatment. One randomized child received corticosteroids intraoperatively and postoperatively for surgical reasons and in another child, the surgeon, immediately before starting the operation, decided to insert tympanostomy tubes but not to perform tonsillectomy. Both of these children were excluded from all analyses. Baseline characteristics were similar in the study groups except that children assigned to dexamethasone, 0.05 mg/kg, received nitrous oxide less often (TABLE 1). Six randomized children were lost to follow-up after they had left the hospital on day 1.

Postoperative Nausea and Vomiting

Twenty-four hours after surgery, 24 of the 54 children who received placebo experienced at least 1 episode of PONV (44%; 95% confidence interval [CI], 31%-59%) as did 20 of 53 children who received dexamethasone, 0.05 mg/kg (38%; 95% CI, 25%-52%), 13 of 54 children who received dexamethasone, 0.15 mg/kg (24%; 95% CI, 13%-38%), and 6 of 52 children who received dexamethasone, 0.5 mg/kg (12%; 95% CI, 4%-23%) ($P < .001$) (TABLE 2). Age and nitrous oxide use were positive confounders. The dose response was significant in crude and multivariate analyses and was confirmed when postoperative vomiting only and the need for rescue antiemetics were analyzed. Twenty-one children started vomiting after the 24th hour; in 6, the last vomiting episode was on the third postoperative day.

Table 2. Rates of Postoperative Nausea and Vomiting and Need for Rescue Antiemetic (0-24 Hours)

	No./Total (%)	Relative Risk (95% Confidence Interval) ^a		P Value ^c	P Value for Linear Trend ^d
		Unadjusted	Adjusted ^b		
Postoperative nausea and/or vomiting					
Placebo	24/54 (44)	1 [Reference]	1 [Reference]	.001	<.001
Dexamethasone, mg/kg					
0.05	20/53 (38)	0.85 (0.54-1.34)	0.98 (0.57-1.42)		
0.15	13/54 (24)	0.54 (0.31-0.95)	0.65 (0.33-1.10)		
0.5	6/52 (12)	0.26 (0.11-0.58)	0.27 (0.10-0.63)		
Postoperative vomiting only					
Placebo	23/54 (43)	1 [Reference]	1 [Reference]	.003	.002
Dexamethasone, mg/kg					
0.05	12/53 (23)	0.53 (0.29-0.95)	0.64 (0.32-1.04)		
0.15	12/54 (22)	0.52 (0.29-0.93)	0.67 (0.35-1.07)		
0.5	5/52 (10)	0.23 (0.09-0.55)	0.27 (0.10-0.63)		
Need for rescue antiemetic ^e					
Placebo	11/54 (20)	1 [Reference]	1 [Reference]	.04	.04
Dexamethasone, mg/kg					
0.05	4/53 (8)	0.37 (0.12-1.09)	0.39 (0.12-1.17)		
0.15	3/54 (6)	0.27 (0.08-0.92)	0.35 (0.10-1.17)		
0.5	2/52 (4)	0.19 (0.04-0.81)	0.17 (0.04-0.79)		

^aRelative risks compare each dexamethasone group with placebo.

^bAdjusted for age, nitrous oxide, and exposure to morphine in the postanesthetic care unit. Adjusting for neostigmine did not change the point estimates and decreased the goodness of fit of the model.

^cP value by likelihood ratio test comparing a multivariate model including dexamethasone dose with a nested model excluding this variable.

^dP value by Wald test on the logistic regression coefficient considering dexamethasone dose as a continuous variable (calculated when the P value of the likelihood ratio test testing departure from linear trend was $> .10$).

^eRescue antiemetic was ondansetron. Hosmer-Lemeshow test for goodness of fit (10 quantiles) for the adjusted models was 0.98 for postoperative nausea and/or vomiting, 0.48 for postoperative vomiting only, and 0.72 for need for rescue antiemetic.

Table 3. Pain Outcomes

	No./Total (%)	Relative Risk (95% Confidence Interval) ^a		P Value ^c
		Unadjusted	Adjusted ^b	
Need for morphine in postanesthetic care unit				
Placebo	42/54 (78)	1 [Reference]	1 [Reference]	.42
Dexamethasone, mg/kg				
0.05	42/53 (79)	1.02 (0.83-1.24)	0.99 (0.72-1.15)	
0.15	36/54 (67)	0.86 (0.68-1.09)	0.83 (0.54-1.05)	
0.5	37/52 (71)	0.91 (0.73-1.14)	0.92 (0.64-1.11)	
Need for ibuprofen during first 24 h				
Placebo	35/54 (65)	1 [Reference]	1 [Reference]	.01
Dexamethasone, mg/kg				
0.05	20/53 (38)	0.58 (0.39-0.87)	0.55 (0.32-0.86)	
0.15	23/54 (43)	0.66 (0.45-0.95)	0.63 (0.37-0.94)	
0.5	20/52 (38)	0.59 (0.40-0.88)	0.59 (0.33-0.89)	
Adequate pain relief during first 24 h ^d				
Placebo	13/54 (24)	1 [Reference]	1 [Reference]	.37
Dexamethasone, mg/kg				
0.05	17/52 (33)	1.36 (0.73-2.51)	1.43 (0.75-2.31)	
0.15	16/54 (30)	1.23 (0.66-2.30)	1.23 (0.62-2.07)	
0.5	10/51 (20)	0.81 (0.39-1.69)	0.82 (0.36-1.61)	

^aRelative risks compare each dexamethasone group with placebo.

^bAdjusted for technique of surgery. Adjusting for duration of surgery did not change the point estimate or decreased goodness of fit of the model.

^cP value by likelihood ratio test comparing a multivariate model including dexamethasone dose with a nested model excluding this variable.

^dVisual analog scale or revised Faces Pain Scale scores of less than 3 out of 10 or Children of Eastern Ontario Pain Scale scores of less than 8 out of 14. Hosmer-Lemeshow goodness-of-fit test (8 quantiles) was greater than 0.75 for all adjusted models.

Postoperative Analgesia

Children who received dexamethasone received ibuprofen significantly less often as a rescue analgesic during the first 24 hours, independent of the dose of dexamethasone (TABLE 3). This was still true after adjustment for surgical technique. Dexamethasone did not decrease the need for morphine in the postanesthetic care unit nor did it decrease the proportion of children with inadequate pain relief during the first 24 hours.

Further Outcomes

Serum glucose levels at the end of surgery, quality of sleep during the first night, satisfaction levels of nurses and parents, delay until first oral intake, and the number of children who received antibiotics during the study period were similar among groups.

Postoperative Hemorrhage

Among the 6 children who were lost to follow-up, none had a bleeding episode during the first 24 hours. Among the remaining 207 children, 22 (10.6%; 95% CI, 6.8%-15.6%) experienced at least 1 bleeding episode; 4 had 2 episodes. All episodes occurred within the 10-day study follow-up except 1 category 1 episode that was diagnosed retrospectively through chart review and that had occurred on postoperative day 20 (TABLE 4; FIGURE 2). Fifteen children (68.2% [95% CI, 45.1%-86.1%] of those bleeding) had bleeding diagnosed later than the first postoperative day.

Two of the 53 children who received placebo (4%; 95% CI, 0.5%-13%), 6 of 53 (11%; 95% CI, 4%-23%) who received dexamethasone, 0.05

mg/kg, 2 of 51 (4%; 95% CI, 0.5%-13%) who received dexamethasone, 0.15 mg/kg, and 12 of 50 (24%; 95% CI, 13%-38%) who received dexamethasone, 0.5 mg/kg, had at least 1 bleeding episode ($P=.003$) (TABLE 5). Age was significantly associated with bleeding risk and was a negative confounder of the association. The largest dose of dexamethasone was associated with the highest risk of bleeding in crude and adjusted analyses. Eight children needed emergency reoperation because of posttonsillectomy hemorrhage (bleeding category 3); they had all received dexamethasone (Table 4). With the largest dose of dexamethasone, the risk was highest, although the difference compared with placebo was only borderline significant ($P=.05$).

Table 4. Characteristics of All 22 Children Who Had a Bleeding Episode

Patient No./Sex/Age, y	Bleeding Category ^a			Received Ibuprofen Before Bleeding	No. of Bleeding Episodes/Surgeries for That Surgeon	Indication for Surgery	Surgical Technique ^b
	1	2	3				
Placebo							
125/M/4 ^c	Day 4			Yes	3/24	OSA	Combined
215/M/9		Day 3		Yes	6/36	OSA	Combined
Dexamethasone, 0.05 mg/kg							
47/F/6		Day 0		Yes	6/36	OSA	Combined
53/M/3			Day 7	Yes	1/5	OSA	Hot
84/F/12 ^c			Days 0, 9	No	1/15	OSA, RT	Combined
109/F/4			Day 1	No	6/36	OSA, RT	Combined
120/M/6		Day 1		Yes	3/17	OSA, RT	Combined
203/M/4	Day 5			Yes	2/15	OSA	Hot
Dexamethasone, 0.15 mg/kg							
49/M/4			Day 10	Yes	2/19	OSA	Hot
106/F/11	Day 7			Yes	1/7	OSA	Combined
Dexamethasone, 0.5 mg/kg							
3/M/4			Day 0	No	3/24	OSA	Combined
13/M/16		Days 7, 9		Yes	6/36	RT	Combined
27/F/6		Day 5		No	2/8	OSA	Hot
40/M/13		Day 7	Day 0	Yes	2/19	RT	Hot
89/F/15		Day 4	Day 6	No	3/17	RT	Combined
123/M/5 ^c	Day 20			No	6/36	OSA, RT	Combined
133/F/9 ^c		Day 8		No	3/17	OSA	Cold
156/M/7	Day 7			Unknown	1/16	OSA	Hot
173/F/9	Day 6			Yes	3/24	RT	Combined
180/F/5	Day 10			Yes	2/15	OSA	Hot
186/F/6	Day 3			Yes	2/8	OSA	Hot
196/F/5			Day 0	No	6/36	RT	Combined

Abbreviations: OSA, obstructive sleep apnea; RT, recurrent tonsillitis.

^aBleeding category 1 indicates history of bleeding but no evidence of bleeding on clinical examination; category 2, evidence of bleeding on clinical examination and no need for reoperation; and category 3, emergency reoperation due to bleeding.

^bSee the "Procedures" section in the "Methods" for a description of the surgical techniques.

^cPatient 84 (bleeding category 3 on day 0) and patient 133 (bleeding category 2 on day 8) had adenoid bleeding on clinical examination. Patient 123 (bleeding category 1 on day 20) and patient 125 (bleeding category 1 on day 4) had anamnestic nose bleeding.

Sensitivity Analyses

Information on body mass index and bleeding was available for 175 children. Twelve children (6.9%) were obese,²³ none of whom had an episode of bleeding. Of the 163 nonobese children, 19 (11.7%) had an episode of bleeding ($P=.21$). For the remaining 3 children with bleeding, body mass index was not available; all had received dexamethasone.

Exposure to ibuprofen at home remained unknown for 23 children because parents failed to fill in the questionnaires. One of these children experienced a bleeding episode; she had received dexamethasone, 0.5 mg/kg. In the sample of children in whom ibuprofen exposure at home was known ($n=190$), exposure did not confound the association and did not increase the fit of the model to the data.

When we assumed that none of the 6 children lost to follow-up had bleeding, the adjusted relative risk for any bleeding with dexamethasone, 0.5 mg/kg, was 6.53 (95% CI, 1.69-16.3) and for bleeding with evidence at clinical examination was 7.67 (95% CI, 1.02-31.7). When we assumed that all children lost to follow-up had bleeding, the adjusted relative risk for any bleeding with dexamethasone, 0.5 mg/kg, was 5.07 (95% CI, 1.70-10.7) and for bleeding with evidence at clinical examination was 4.94 (95% CI, 1.16-14.2).

Surgical Interventions

All interventions were performed by staff surgeons or by residents under the supervision of staff surgeons. Twenty-two surgeons performed the operations; they were equally distributed among the study groups. Children who had bleeding were operated on by 9 surgeons (41% of all surgeons) who performed a total of 162 surgeries (76% of all surgeries). For these 9 surgeons, the median ratio of the number of performed surgeries per number of subsequent bleedings was 7 (range, 4-16) (Table 4).

COMMENT

The 2008 guidelines of the Association of Paediatric Anaesthetists of Great Britain and Ireland conclude that in patients undergoing tonsillectomy, “dexamethasone 0.15 mg/kg provided good reduction in postoperative vom-

iting with no adverse effects.”²⁴ Expert panels have recommended the widespread use of dexamethasone in surgical patients.⁷ Prophylactic dexamethasone has become standard care in children undergoing tonsillectomy in many institutions.^{8-10,12} Several authors

Figure 2. Proportion of Children With an Episode of Bleeding in the First 21 Days After Randomization

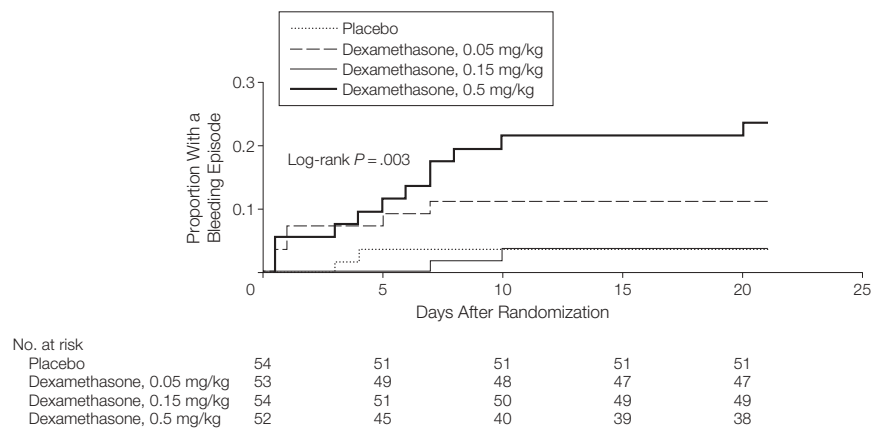


Table 5. Rates of Postoperative Bleeding

		Relative Risk (95% Confidence Interval) ^a		<i>P</i> Value ^c
		Unadjusted	Adjusted ^b	
Any bleeding, with or without evidence at clinical examination				
Placebo	2/53 (4)	1 [Reference]	1 [Reference]	.003
Dexamethasone, mg/kg				
0.05	6/53 (11)	3.00 (0.63-14.2)	3.29 (0.70-11.3)	
0.15	2/51 (4)	1.04 (0.15-7.10)	1.19 (0.16-6.91)	
0.5	12/50 (24)	6.36 (1.50-27.0)	6.80 (1.77-16.5)	
Bleeding with evidence at clinical examination, with or without reoperation				
Placebo	1/53 (2)	1 [Reference]	1 [Reference]	.03
Dexamethasone, mg/kg				
0.05	5/53 (9)	5.00 (0.60-41.4)	5.65 (0.69-27.5)	
0.15	1/51 (2)	1.04 (0.07-16.2)	1.27 (0.08-15.4)	
0.5	7/50 (14)	7.42 (0.95-58.2)	8.04 (1.08-32.1)	
Reoperation due to bleeding				
Placebo	0/53	NA	NA	
Dexamethasone, mg/kg				
0.05	3/53 (6)			.24 ^d
0.15	1/51 (2)			.49 ^d
0.5	4/50 (8)			.05 ^d

Abbreviation: NA, data not applicable (0 events in placebo group).

^aRelative risks compare each dexamethasone group with placebo.

^bAdjusted for age. Adjusting for surgical technique, surgical indication, exposure to nonsteroidal anti-inflammatory drugs during the first 24 hours, or vomiting during the first 24 hours did not change the estimates and did not increase the fit of the model to the data.

^cP Value by likelihood ratio test comparing a multivariate model including dexamethasone dose with a nested model excluding this variable. Hosmer-Lemeshow test for goodness of fit (10 quantiles) was greater than 0.75 for adjusted models.

^dBy Fisher exact test.

have suggested that dexamethasone should be given in considerably higher doses than what we tested.¹³⁻¹⁶

Our trial showed that dexamethasone significantly and dose-dependently decreased the incidence of PONV in children undergoing tonsillectomy. Dexamethasone also decreased the need for rescue analgesia with ibuprofen. However, dexamethasone was associated with a significant increase in the risk of postoperative bleeding.

Observational studies have reported an association between steroid exposure and an increased risk of bleeding in the context of tonsillectomy.^{25,26} A case-control study reported a significant annual 15% increase in posttonsillectomy hemorrhage, and the authors suggested that this may be partially related to the increased use of perioperative steroids.²⁶ A retrospective chart review of 430 tonsillectomy patients found that the use of intraoperative steroids, among other factors, was positively correlated with postoperative bleeding; however, curiously, the authors concluded that the use of steroids could probably be discounted as a causative factor.²⁵

Previously published trials that studied the impact of dexamethasone on PONV in children undergoing tonsillectomy were small^{27,28} or their observation periods were short.^{13,16} If we had restricted our observation period to 24 hours, we would have identified an antiemetic dose response with dexamethasone without any evidence of an increased bleeding risk and concluded that dexamethasone, 0.5 mg/kg, was efficacious and safe.

The association between dexamethasone and increased risk of bleeding was unexpected, and alternative explanations should be explored. Chance is an unlikely explanation for our finding, as reflected by *P* values below the conventional .05 significance level. Selection bias was unlikely too; group assignment was allocated through randomization. Concealment of allocation was ensured by the hospital pharmacy, and anesthesiologists, surgeons, patients,

and investigators were blinded to study treatments.

We explored potential confounding factors. Surgical techniques were equally distributed among groups,²⁹ and we were unable to identify any clustering of the surgeons among the different groups. The baseline risk was not excessively high; similar rates of reoperation after tonsillectomy have been reported before.^{4,5} Also, the distribution of surgical indications was similar in the entire cohort and in the subgroup that had bleeding.

Residual confounding is possible. We cannot rule out that some children had an unrecognized hemostasis disorder. The most common hereditary coagulopathy, von Willebrand disease, affects about 2% of the population.³⁰ Theoretically, about 4 children may have had von Willebrand disease; they may have all received dexamethasone and none placebo. We cannot rule out that a child with von Willebrand disease bled because of the underlying disease rather than the dexamethasone. We abstained from performing preoperative blood tests.¹⁷ However, those with a suspected coagulation disorder or those taking anticoagulants, aspirin, or classic NSAIDs did not undergo tonsillectomy.

Several arguments suggest that the association between dexamethasone and bleeding should be considered causal. Reverse causality can be excluded. The magnitude of the association was strong; with the largest dose of dexamethasone, the bleeding risk appeared to be 4 times higher than the risk associated with classic NSAIDs.^{4,5} A biological basis for the increased bleeding risk would support causality. Dexamethasone was shown to interfere with platelet aggregation in animals,³¹ but in humans, glucocorticosteroids did not impair platelet function or primary hemostasis.³² An increased bleeding risk associated with dexamethasone in the absence of a preliminary lesion seems unlikely. In infants with bronchiolitis who received high doses of dexamethasone, no bleeding was reported.³³ Con-

comitant use of NSAIDs may have reinforced the bleeding risk. The risk of gastrointestinal hemorrhage in patients taking classic NSAIDs is largely increased by concomitant glucocorticosteroids.³⁴ One of our initial hypotheses was that children who were exposed to dexamethasone would need less NSAIDs postoperatively and, subsequently, would be less prone to bleeding. Yet the risk of bleeding was increased in children who received dexamethasone although they were significantly less frequently exposed to ibuprofen. This observation further strengthens the additional bleeding risk that is associated with dexamethasone.

The most convincing biological explanation might be related to inhibition of repair processes of wounds by glucocorticosteroids³⁵ and to delayed ulcer healing.³⁶ Ulcer healing is a programmed and complex repair process.^{35,37} Epidermal and basic fibroblast growth factors regulate the process of mucosal healing and are inhibited by dexamethasone.³⁸⁻⁴⁰ Dexamethasone decreases collagen deposition, epithelialization, and fibroblast content of surgical wounds.⁴¹ This would explain why bleeding sometimes occurred several days after administration of dexamethasone.

Dose responsiveness for the bleeding potency of dexamethasone would further support causality. There was no evidence against a statistically significant linear trend for any bleeding. However, with the lowest dose, the risk appeared to be greater than with the medium dose. This observation has both methodological and clinical implications. First, absence of a consistent dose response does not necessarily mean that there is none. Our trial was designed to test the antiemetic dose response of dexamethasone; the doses were chosen accordingly. Lower doses need to be tested to identify a possible bleeding-inducing dose response of dexamethasone. The clinical message is that we cannot conclude with confidence that dexamethasone doses below 0.5 mg/kg are safe.

The problem of early termination of our trial should not be disregarded.^{42,43} Stopping early for evidence of harm has the same potential to exaggerate the magnitude of harm as would stopping early for benefit to exaggerate the magnitude of benefit. Against these methodological constraints, ethical issues needed to be weighed. We considered it unacceptable to continue recruiting children in this context.

Tonsillectomy is not comparable with most other surgical interventions because the wound created by the excision of the tonsils is neither sutured nor covered by sealing or hemostatic material. It remains a large wound surface, which is covered by crusting and exposed to food, inhaled air, and saliva. The vascular supply of the tonsils is rich. Posttonsillectomy hemorrhage is a potentially lethal complication because the upper airways are unprotected and manual compression is nearly impossible. If hemorrhage does not stop spontaneously, reoperation is unavoidable. Blood loss becomes evident only when the child is hemodynamically unstable or vomits the swallowed blood.⁴⁴

In summary, in children undergoing tonsillectomy, dexamethasone has a significant and dose-dependent antiemetic effect and decreases the need for rescue analgesia with NSAIDs. However, it cannot be excluded that dexamethasone, possibly through inhibition of wound healing, increases the risk of postoperative bleeding in this specific setting. Randomized trials that are specifically designed to confirm or refute our findings are needed, although it may be difficult to perform such trials in children. Future trials should involve several centers to improve the applicability of the results. In the meantime, and even though dexamethasone is a potent antiemetic drug, it may be prudent to avoid it in children undergoing tonsillectomy.

Author Contributions: Dr Tramèr had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Czarnetzki, Elia, Lysakowski, Dumont, Landis, Giger, Dulguerov, Desmeules, Tramèr.

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Critical revision of the manuscript for important intellectual content: Czarnetzki, Elia, Lysakowski, Dumont, Landis, Giger, Dulguerov, Desmeules, Tramèr.

Statistical analysis: Elia.

Obtained funding: Czarnetzki, Tramèr.

Administrative, technical, or material support: Czarnetzki, Dumont, Landis, Giger, Tramèr.

Study supervision: Tramèr.

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REFERENCES

1. Van Den Akker EH, Hoes AW, Burton MJ, Schilder AG. Large international differences in (adeno) tonsillectomy rates. *Clin Otolaryngol Allied Sci*. 2004; 29(2):161-164.
2. Russo CA, Owens P, Steiner C, Josephsen J. *Ambulatory Surgery in US Hospitals, 2003: HCUP Fact Book No. 9*. Rockville, MD: Agency for Healthcare Research and Quality; January 2007. AHRQ publication 07-0007. <http://www.ahrq.gov/data/hcup/factbk9/>. Accessed August 10, 2008.
3. Hilton M. Tonsillectomy technique—tradition versus technology. *Lancet*. 2004;364(9435):642-643.
4. Marret E, Flahault A, Samama CM, Bonnet F. Effects of postoperative, nonsteroidal anti-inflammatory drugs on bleeding risk after tonsillectomy: meta-analysis of randomized controlled trials. *Anesthesiology*. 2003;98(6):1497-1502.
5. Meinihe S, Rømsing J, Dahl JB, Tramèr MR. Nonsteroidal anti-inflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. *Anesth Analg*. 2003;96(1):68-77.
6. Henzi I, Walder B, Tramèr MR. Dexamethasone for the prevention of postoperative nausea and vomit-

ing: a quantitative systematic review. *Anesth Analg*. 2000;90(1):186-194.

7. Gan TJ, Meyer TA, Apfel CC, et al; Society for Ambulatory Anesthesia. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2007; 105(6):1615-1628.
8. Bolton CM, Myles PS, Nolan T, Sterne JA. Prophylaxis of postoperative vomiting in children undergoing tonsillectomy: a systematic review and meta-analysis. *Br J Anaesth*. 2006;97(5):593-604.
9. Afman CE, Welge JA, Steward DL. Steroids for post-tonsillectomy pain reduction: meta-analysis of randomized controlled trials. *Otolaryngol Head Neck Surg*. 2006;134(2):181-186.
10. Steward DL, Welge JA, Myer CM. Do steroids reduce morbidity of tonsillectomy? meta-analysis of randomized trials. *Laryngoscope*. 2001;111(10):1712-1718.
11. Kehlet H. Glucocorticoids for peri-operative analgesia: how far are we from general recommendations? *Acta Anaesthesiol Scand*. 2007;51(9):1133-1135.
12. Kim MS, Cote CJ, Cristoloveanu C, et al. 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. *Anesth Analg*. 2007; 104(5):1052-1058.
13. April MM, Callan ND, Nowak DM, Hausdorff MA. The effect of intravenous dexamethasone in pediatric adenotonsillectomy. *Arch Otolaryngol Head Neck Surg*. 1996;122(2):117-120.
14. Tom LW, Templeton JJ, Thompson ME, Marsh RR. Dexamethasone in adenotonsillectomy. *Int J Pediatr Otorhinolaryngol*. 1996;37(2):115-120.
15. Pappas AL, Sukhani R, Hotelling AJ, et al. The effect of preoperative dexamethasone on the immediate and delayed postoperative morbidity in children undergoing adenotonsillectomy. *Anesth Analg*. 1998; 87(1):57-61.
16. Hanasono MM, Lalakea ML, Mikulec AA, Shepard KG, Wellis V, Messner AH. Perioperative steroids in tonsillectomy using electrocautery and sharp dissection techniques. *Arch Otolaryngol Head Neck Surg*. 2004;130(8):917-921.
17. Krishna P, Lee D. Post-tonsillectomy bleeding: a meta-analysis. *Laryngoscope*. 2001;111(8):1358-1361.
18. Eckman MH, Erban JK, Singh SK, Kao GS. Screening for the risk for bleeding or thrombosis. *Ann Intern Med*. 2003;138(3):W15-W24.
19. Kujawski O, Dulguerov P, Gysin C, Lehmann W. Microscopic tonsillectomy: a double-blind randomized trial. *Otolaryngol Head Neck Surg*. 1997;117(6):641-647.
20. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain*. 2001;93(2):173-183.
21. McGrath PJ, Gea J. The Children of Eastern Ontario Pain Scale (CHEOPS): a behavioral scale for rating postoperative pain in children. In: Fields HL, Dubner R, Cervero F, eds. *Advances in Pain Research and Therapy*. New York, NY: Raven Press; 1982: 395-402.
22. Tramèr MR. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews, I: efficacy and harm of antiemetic interventions, and methodological issues. *Acta Anaesthesiol Scand*. 2001;45(1):4-13.
23. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320(7244):1240-1243.
24. Association of Paediatric Anaesthetists of Great

- Britain and Ireland. *Guidelines on the Prevention of Post-operative Vomiting in Children*. Spring 2008. http://www.apagbi.org.uk/docs/APA%20Draft_POV_guidelines_%20Jan08.pdf. Accessed August 10, 2008.
25. Collison PJ, Mettler B. Factors associated with post-tonsillectomy hemorrhage. *Ear Nose Throat J*. 2000;79(8):640-642, 644, 646.
 26. Macassey EA, Baguley C, Dawes P, Gray A. 15-year audit of post-tonsillectomy haemorrhage at Dunedin Hospital. *ANZ J Surg*. 2007;77(7):579-582.
 27. Catlin FI, Grimes WJ. The effect of steroid therapy on recovery from tonsillectomy in children. *Arch Otolaryngol Head Neck Surg*. 1991;117(6):649-652.
 28. Ohlms LA, Wilder RT, Weston B. Use of intraoperative corticosteroids in pediatric tonsillectomy. *Arch Otolaryngol Head Neck Surg*. 1995;121(7):737-742.
 29. Lowe D, van der Meulen J; National Prospective Tonsillectomy Audit. Tonsillectomy technique as a risk factor for postoperative haemorrhage. *Lancet*. 2004;364(9435):697-702.
 30. Mannucci PM. Treatment of von Willebrand's disease. *N Engl J Med*. 2004;351(7):683-694.
 31. van Giezen JJ, Brakkee JG, Dreteler GH, Bouma BN, Jansen JW. Dexamethasone affects platelet aggregation and fibrinolytic activity in rats at different doses which is reflected by their effect on arterial thrombosis. *Blood Coagul Fibrinolysis*. 1994;5(2):249-255.
 32. Thong KL, Mant MJ, Grace MG. Lack of effect of prednisone administration on bleeding time and platelet function of normal subjects. *Br J Haematol*. 1978;38(3):373-380.
 33. Corneli HM, Zorc JJ, Majahan P, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis [published correction appears in *N Engl J Med*. 2008;359(18):1972]. *N Engl J Med*. 2007;357(4):331-339.
 34. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of non-steroidal anti-inflammatory drugs. *Ann Intern Med*. 1991;114(9):735-740.
 35. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. *N Engl J Med*. 2005;353(16):1711-1723.
 36. Carpani de Kaski M, Rentsch R, Levi S, Hodgson HJ. Corticosteroids reduce regenerative repair of epithelium in experimental gastric ulcers. *Gut*. 1995;37(5):613-616.
 37. Luo JC, Chi CW, Lin HY, et al. Dexamethasone inhibits epidermal growth factor-stimulated gastric epithelial cell proliferation. *J Pharmacol Exp Ther*. 2007;320(2):687-694.
 38. Tarnawski A, Stachura J, Durbin T, Sarfeh IJ, Gergely H. Increased expression of epidermal growth factor receptor during gastric ulcer healing in rats. *Gastroenterology*. 1992;102(2):695-698.
 39. Szabo S, Khomenko T, Gombos Z, Deng XM, Jadus MR, Yoshida M. Review article: transcription factors and growth factors in ulcer healing. *Aliment Pharmacol Ther*. 2000;14(suppl 1):33-43.
 40. Chakraborti S, Mandal M, Das S, Mandal A, Chakraborti T. Regulation of matrix metalloproteinases: an overview. *Mol Cell Biochem*. 2003;253(1-2):269-285.
 41. Durmus M, Karaaslan E, Ozturk E, et al. The effects of single-dose dexamethasone on wound healing in rats. *Anesth Analg*. 2003;97(5):1377-1380.
 42. Montori VM, Devereaux PJ, Adhikari NK, et al. Randomized trials stopped early for benefit: a systematic review. *JAMA*. 2005;294(17):2203-2209.
 43. Nissen SE. ADAPT: the wrong way to stop a clinical trial. *PLoS Clin Trials*. 2006;1(7):e35.
 44. Windfuhr JP, Chen YS, Remmert S. Hemorrhage following tonsillectomy and adenoidectomy in 15,218 patients. *Otolaryngol Head Neck Surg*. 2005;132(2):281-286.

Many of the brain's remaining mysteries need for solution mere wiring diagrams; yet a metaphysical halo lingers about the mystery of self-consciousness. A computer, after all, of sufficient complexity could handle the stimuli and responses of living without any component that says "I." But within the human—and, dare we think, the cetacean and simian?—brain there is a watcher, who always recedes, and who answers every question with another question.

—John Updike (1932-)