

# Perioperative Dexamethasone Administration and Risk of Bleeding Following Tonsillectomy in Children

## A Randomized Controlled Trial

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**A**DENOTONSILLECTOMY IS EXCEEDINGLY common, with a reported increase in tonsillectomy rates in children younger than 15 years from 287 000 to 530 000 per year over the past decade.<sup>1,2</sup> Although safe, adenotonsillectomy can result in significant complications, such as aspiration, pulmonary edema, postoperative dehydration, and hemorrhage.<sup>3</sup> Although complications are infrequent because tonsillectomy is so common, the absolute number of children experiencing tonsillectomy complications is formidable.

Postoperative nausea and vomiting (PONV) is a major source of morbidity following tonsillectomy. Perioperative administration of corticosteroids effectively manages PONV and also results in more rapid resumption of a diet, improved pain control, and decreased airway swelling.<sup>4</sup> The benefits

**Context** Corticosteroids are commonly given to children undergoing tonsillectomy to reduce postoperative nausea and vomiting; however, they might increase the risk of perioperative and postoperative hemorrhage.

**Objective** To determine the effect of dexamethasone on bleeding following tonsillectomy in children.

**Design, Setting, and Patients** A multicenter, prospective, randomized, double-blind, placebo-controlled study at 2 tertiary medical centers of 314 children aged 3 to 18 years undergoing tonsillectomy without a history of bleeding disorder or recent corticosteroid medication use and conducted between July 15, 2010, and December 20, 2011, with 14-day follow-up. We tested the hypothesis that dexamethasone would not result in 5% more bleeding events than placebo using a noninferiority statistical design.

**Intervention** A single perioperative dose of dexamethasone (0.5 mg/kg; maximum dose, 20 mg), with an equivalent volume of 0.9% saline administered to the placebo group.

**Main Outcome Measures** Rate and severity of posttonsillectomy hemorrhage in the 14-day postoperative period using a bleeding severity scale (level I, self-reported or parent-reported postoperative bleeding; level II, required inpatient admission for postoperative bleeding; or level III, required reoperation to control postoperative bleeding).

**Results** One hundred fifty-seven children (median [interquartile range] age, 6 [4-8] years) were randomized into each study group, with 17 patients (10.8%) in the dexamethasone group and 13 patients (8.2%) in the placebo group reporting bleeding events. In an intention-to-treat analysis, the rates of level I bleeding were 7.0% (n=11) in the dexamethasone group and 4.5% (n=7) in the placebo group (difference, 2.6%; upper limit 97.5% CI, 7.7%; *P* for noninferiority=.17); rates of level II bleeding were 1.9% (n=3) and 3.2% (n=5), respectively (difference, -1.3%; upper limit 97.5% CI, 2.2%; *P* for noninferiority<.001); and rates of level III bleeding were 1.9% (n=3) and 0.6% (n=1), respectively (difference, 1.3%; upper limit 97.5% CI, 3.8%; *P* for noninferiority=.002).

**Conclusions** Perioperative dexamethasone administered during pediatric tonsillectomy was not associated with excessive, clinically significant level II or III bleeding events based on not having crossed the noninferior threshold of 5%. Increased subjective (level I) bleeding events caused by dexamethasone could not be excluded because the noninferiority threshold was crossed.

**Trial Registration** clinicaltrials.gov Identifier: NCT01415583

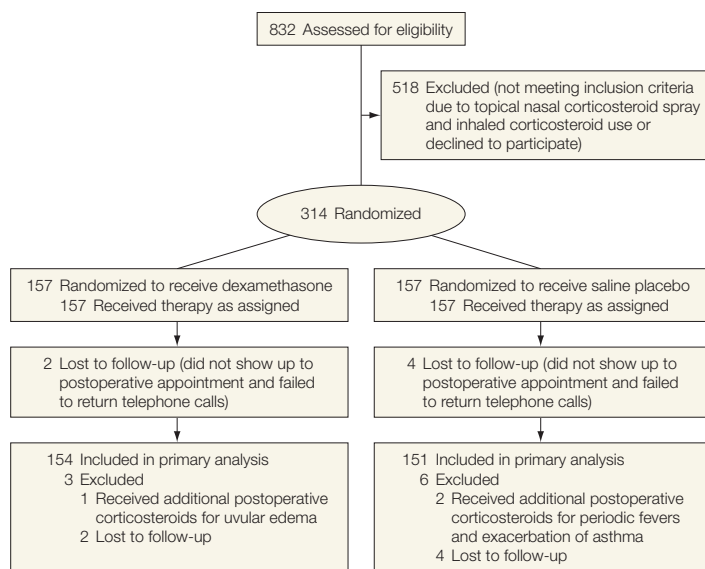
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**Figure 1.** Participant Flow of Patients

of corticosteroid administration have been known for many years.<sup>5</sup> Two meta-analyses demonstrated the benefits of a single dose of dexamethasone in controlling PONV following tonsillectomy.<sup>6,7</sup> Consequently, the American Academy of Otolaryngology–Head and Neck Surgery Clinical Practice Guideline on pediatric tonsillectomy provided a strong recommendation for the use of perioperative corticosteroid therapy.<sup>8</sup>

A recent randomized trial studying the dose response of perioperative dexamethasone to PONV in children undergoing tonsillectomy was prematurely terminated due to an increased risk of postoperative hemorrhage.<sup>9</sup> The outcomes of the trial suggested that a single dose of intraoperative dexamethasone significantly increased posttonsillectomy hemorrhage events. In light of these findings, there is a need to reassess the safety profile for dexamethasone when used during tonsillectomy.

Given the long history of dexamethasone use during tonsillectomy and the single report questioning its safety, we performed a clinical trial to address concerns about bleeding events in children associated with dexamethasone use during tonsillectomy.

## METHOD

### Study Design and Conduct

Our study was reviewed and approved by the institutional review boards of both institutions (Massachusetts Eye and Ear Infirmary, Boston, and Naval Medical Center San Diego, San Diego, California). All patients, their guardians, or both provided written informed consent and assent. Our study was designed as a prospective, randomized, double-blind, placebo-controlled, noninferiority trial. Randomization was performed by the hospital pharmacist and occurred via a 1:1 scheme using a random number generator. On the day of surgery, a syringe containing either dexamethasone (0.5 mg/kg; maximum dose, 20 mg) or volume-equivalent 0.9% normal saline was then delivered to the anesthesiologist. Both the study drug and placebo were in identical packaging. The study drug was administered parenterally at the start of the operation. All nurses, anesthesiologists, surgeons, patients, patient guardians, and data collectors were blinded as to whether the patient received the dexamethasone or 0.9% normal saline.

The operation and postoperative care were standardized. All patients received

a single dose of parenteral perioperative antibiotics. All tonsillectomies were performed in an extracapsular fashion using monopolar electrocautery (12 W fulgurate) and a spatula-tip. Bleeding was controlled with suction cautery (12–15 W fulgurate). Postoperatively, study patients did not receive any dexamethasone. Analgesic strategies consisted of acetaminophen with or without codeine or hydrocodone, depending on age, severity of pain, and surgical indication. Ibuprofen and any other nonsteroidal anti-inflammatory drugs were not prescribed during the postoperative period. Ondansetron was administered intraoperatively for nausea as a single parenteral dose. Promethazine was administered parenterally every 6 hours as needed for breakthrough nausea. Patients were prescribed oral antibiotics postoperatively for 5 days.

All patients had strict discharge instructions to return to the emergency department of the medical center for any signs of postoperative bleeding. On or shortly after postoperative day 14, the patient and their guardian completed a bleeding questionnaire (eMethods, available at <http://www.jama.com>) that was reviewed and recorded into a secure database.

The data safety and monitoring board performed an interim analysis after approximately 50% of the patients had been enrolled and their postoperative data collected, and concluded the data did not meet criteria for stopping the trial.

### Study Patients

Eligible patients aged between 3 and 18 years underwent tonsillectomy by electrocautery for the indication of sleep disordered breathing or infectious tonsillitis at 2 academic medical centers (Massachusetts Eye and Ear Infirmary and Naval Medical Center San Diego). Exclusion criteria included a known personal or family history of any bleeding disorder; use of corticosteroid medications within 2 weeks of surgery, including topical nasal corticosteroids; and use of an alternative surgical technique (FIGURE 1).

### Outcome Measures

The primary outcome measure for the trial was postoperative bleeding stratified by severity and is defined in the BOX. Secondary outcomes included postoperative bleeding rate stratified by age, indication for surgery, type of surgery, and surgeon.

### Power Calculation

The EAST statistical software program (Cytel Inc) was used to calculate the sample size assuming a power of 90%,  $\alpha = .25$ , and an interim analysis at 50% of patient accrual, with early stopping for increased bleeding rates in the dexamethasone group. The primary noninferiority hypothesis required that the dexamethasone group had no more than a 5% absolute increase in the rate of bleeding compared with the placebo group. Our calculated necessary sample size was 298 patients (149 in the dexamethasone group and 149 in the placebo group). The sample size was increased to 305 after factoring in the stopping criteria for the interval analysis.

The noninferiority margin of 5% was determined by several methods. The first method was to query the authors about what they thought an acceptable difference in bleeding rates would be between the corticosteroid and saline groups. At the institution of the senior author (C.J.H.) where a majority of the cases were performed, the pediatric posttonsillectomy bleeding rate was 2.5% from their 2010 quality and outcome report. The US national benchmark is 2.2% to 7.8%. The authors believed we should not exceed the upper limit of the US benchmark, a difference of approximately 5%. A recent commentary<sup>10</sup> on posttonsillectomy hemorrhage discussed "normal" bleeding rates (defined as mean plus 2 SDs) of 4.5% (mean) plus 9.4% (2 SDs), suggesting a maximum bleeding rate of 13.9%. Our 5% margin is within this parameter. In addition, we reviewed the literature for studies in which posttonsillectomy bleeding was an objective (primary or secondary) and the methods section discussed use (or not use) of perioperative corticosteroids.<sup>9,11-20</sup> We found that studies

using perioperative corticosteroids had a 2.8% higher mean bleeding rate than those studies that did not use corticosteroids. The authors believe anything more than double that margin, approximately 5%, would be unsafe.

### Statistical Analysis

A noninferiority study was chosen to demonstrate that dexamethasone was not associated with a clinically significant increase in postoperative bleeding rate compared with placebo in children undergoing tonsillectomy. Consistent with the noninferiority design, the null hypothesis states that the bleeding rate in patients receiving perioperative dexamethasone differed from the bleeding rate in patients receiving perioperative placebo; the alternative hypothesis states that the bleeding rate with dexamethasone is not greater than placebo by more than the noninferiority margin. This noninferiority margin was set at 5%, meaning a difference in bleeding rates that did not exceed 5% would be taken as evidence that the bleeding with dexamethasone is not greater than that with placebo by more than 5%.

The overall significance level was .025 for a 1-sided test; sample size was such that the power to detect the difference of 5% was 0.90. This study was designed as a group sequential trial, with an interim look at 50% information (which in this setting is 50% accrual). Sample size calculations assuming an O'Brien-Fleming spending function specified the need to recruit a total of 305 patients to this study. Sample size was inflated by 5% to accommodate the expected dropout rate, thus increasing the total number of patients to 320.

The interim analysis was performed by testing the difference in level III bleeding rates between the groups and by constructing confidence intervals around the difference in the proportions of children experiencing bleeding. Using the EAST software, it was determined that at the interim analysis, one would test the alternative hypothesis of equivalent rates of bleeding if  $P$  value for testing for a difference in

### Box. Severity Levels of Bleeding

I. All children who reported to have any history of postoperative hemorrhage, whether or not there was clinical evidence.

II. All children who required inpatient admission for postoperative hemorrhage regardless of the need for operative intervention. This level excludes children undergoing evaluation in the emergency department for reported postoperative hemorrhage who had no evidence of clot formation or hemorrhage and were deemed safe for discharge.

III. All children who required return to the operating department for control of postoperative bleeding.

bleeding rates was .0015 or smaller. Using the confidence interval approach, we concluded that dexamethasone increases the rate of bleeding over placebo if the confidence interval for the difference in rates had an upper bound greater than 5%.

Baseline characteristics were compared using the  $\chi^2$ , Fisher exact, or Wilcoxon rank sum tests. A 1-sided confidence interval approach was used to compare the bleeding rate between the 2 groups. The primary analysis was performed on an intention-to-treat basis, where participants lost to follow-up were included and presumed to be not having bleeding episodes. The per-protocol analysis was also performed. Adjusted analysis was also performed obtaining a difference in predicted probabilities of bleeding between the 2 groups by use of logistic regression. Analyses were performed on an intention-to-treat and per-protocol basis. SAS version 9.2 (SAS Institute) was used and  $P < .05$  was considered statistically significant.

### RESULTS

A total of 314 patients were enrolled between July 15, 2010, and December 20, 2011 (Figure 1). The trial ended once data from at least 305 patients had been recorded. One hundred fifty-seven pa-

**Table 1.** Characteristics of Study Patients<sup>a</sup>

Characteristics	Dexamethasone (n = 157)	Saline (n = 157)	P Value
Age, median (IQR), y	6 (4-9)	6 (4-8)	.19
Male sex	88 (56.1)	82 (52.2)	.50
Reason for surgery			
Obstructive sleep apnea	127 (80.9)	125 (79.6)	.87
Tonsillitis	16 (10.2)	14 (8.9)	
Obstructive sleep apnea and tonsillitis	13 (8.3)	17 (10.8)	
Other <sup>b</sup>	1 (0.6)	1 (0.6)	
Surgery type			
Tonsillectomy	16 (10.2)	15 (9.6)	>.99
Tonsillectomy and adenoidectomy	141 (89.8)	141 (89.8)	
Revision tonsillectomy	0 (0)	1 (0.6)	
Operating surgeon			
Surgeon 1	8 (5.1)	9 (5.7)	.79
Surgeon 2	2 (1.3)	2 (1.3)	
Surgeon 3	72 (45.9)	82 (52.2)	
Surgeon 4	60 (38.2)	50 (31.9)	
Surgeon 5	15 (9.5)	14 (8.9)	

Abbreviation: IQR, interquartile range.

<sup>a</sup>Data are shown as No. (%) unless otherwise specified. Obstructive sleep apnea included obstructive sleep apnea, adenotonsillar hypertrophy, hypertrophy, sleep disordered breathing, and snoring. Tonsillitis included tonsillitis, recurrent tonsillitis, chronic tonsillitis, recurrent pharyngitis, and peritonsillar abscess.

<sup>b</sup>Included symptomatic uvular edema or a diagnosis of periodic fevers, aphthous stomatitis, pharyngitis, and adenitis.

tients were randomly assigned to receive placebo and 157 patients were randomly assigned to receive dexamethasone. TABLE 1 shows patient demographics, surgical indications, surgeries performed, and operating surgeon. Six patients (1.9%) were lost to follow-up (2 patients from the dexamethasone group and 4 patients from the placebo group).

Three patients (1.0%) received postoperative corticosteroids in addition to the study medication (1 patient from the dexamethasone group and 2 from the placebo group). Two of the 3 patients received a single dose either for symptomatic uvular edema or periodic fevers (1 patient carried a diagnosis of periodic fevers, aphthous stomatitis, pharyngitis, and adenitis). One patient in the saline group received postoperative corticosteroids on the day of surgery for 5 days due to exacerbation of asthma.

Seventeen patients in the dexamethasone group reported bleeding events (11 patients with level I, 3 with level II, and 3 with level III bleeding events were reported). Thirteen patients in the placebo group reported bleeding events (7 patients with level I, 5 with level II, and 1 with level III bleeding events were

reported). One patient in the placebo group had multiple bleeding events (a level II bleed on postoperative day 12 and a level III bleed on postoperative day 16) and was counted as level II bleeding. The overall rate of bleeding events for all levels was 30 out of 314 (9.6%; 95% CI, 6.5%-13.4%).

Four patients had primary bleeding events, which are defined as occurring within 24 hours of surgery. Two patients were from the dexamethasone group (1 patient with level II bleeding and 1 with level III bleeding) and 2 patients were from the placebo group (both were level II bleeding).

Our intention-to-treat analysis and per-protocol analysis demonstrated similar results (TABLE 2). The dexamethasone treatment failed to show noninferiority for the level I bleeding, but did demonstrate that the bleeding rate with dexamethasone is not more than 5% greater than that with placebo (noninferiority) for both level II and level III bleeding events. The data was stratified for primary vs secondary bleeding events and a decrease in level II and level III bleeding events in both groups was noted. TABLE 3 shows the per-protocol analysis excluding the 6

patients who were lost to follow-up and the 3 patients who received postoperative corticosteroids (including the 4 patients who experienced primary bleeding events).

Secondary analysis was performed to evaluate bleeding rates by age, indication, surgery type, and surgeon. When stratified for the above criteria, there was no significant association found with the more clinically important level II and III bleeding events. Age was found to be unevenly distributed for level I bleeding; therefore, age-adjusted analysis was conducted for level I bleeding. Predicted probability of level I bleeding was estimated for both treatments by setting for a mean age of 6.7 years. The dexamethasone treatment failed to show noninferiority for the level I bleeding after adjusting for age difference (FIGURE 2).

There were no deaths or adverse event outcomes involving any of the study patients.

## COMMENT

Perioperative dexamethasone use in pediatric tonsillectomy is a common practice with strong support in the literature. A Cochrane review deemed dexamethasone “effective and relatively safe” and strongly recommended its use as a single perioperative dose. Clinical practice guidelines from the American Academy of Otolaryngology–Head and Neck Surgery also recommend this practice.<sup>8,21</sup> However, there are concerns about bleeding complications associated with dexamethasone use in tonsillectomy. Posttonsillectomy bleeding rates of 6.1% were reported in patients “injected with topical vasoconstrictors and corticosteroids” compared with 1.8% in the patients not injected with either drugs.<sup>11</sup> An audit of posttonsillectomy hemorrhage showed increased bleeding rates following initiation of corticosteroids, nonsteroidal anti-inflammatory drugs, and bipolar diathermy.<sup>22</sup> Both of these studies were retrospective and could not control confounding factors that might also be responsible for postoperative bleeding. A prospective trial of perioperative corti-

steroids reported deleterious effects of corticosteroids on children undergoing tonsillectomy.<sup>9</sup> It appeared that dexamethasone was associated with an increased risk of postoperative bleeding. However, because posttonsillectomy bleeding was not the primary outcome variable, the study did not have sufficient statistical power to convincingly demonstrate that the corticosteroids caused postoperative hemorrhage. Additionally, surgical techniques were not standardized and there was an unexpectedly large number of primary bleeding events.<sup>12,23</sup>

We designed our trial to definitively resolve the question of dexamethasone causing postoperative bleeding following tonsillectomy in children. We selected a dose of 0.5 mg/kg up to a maximum of 20 mg because it was the preferred dose used clinically by the study authors. This dose was associated with significant bleeding in the study by Czarnetzki et al.<sup>9</sup> A recent meta-analysis<sup>24</sup> of prospective studies of dexamethasone use in pediatric tonsillectomy found a significantly increased odds of bleeding when stratifying for dose ranges of 0.4 mg/kg to 0.6 mg/kg.

A noninferiority study design was chosen to demonstrate that dexamethasone does not increase bleeding rates more than placebo by the prespecified noninferiority margin of 5%. To review, a noninferiority trial (1-sided test) rejects the null hypothesis that there is a difference between the 2 groups. This method is different from an equivalence study (2-sided test) and the opposite of a traditional superiority study where the null hypothesis assumes no difference between the 2 groups. Our outcome of interest was postoperative bleeding in the dexamethasone group. We hypothesized that there would not be more bleeding events in the dexamethasone group compared with the saline placebo group. It was not necessary to perform a 2-sided equivalence trial showing a dexamethasone association with either more or fewer bleeding events than saline placebo because we did not hypothesize any protective effect of dexamethasone against bleeding.

Posttonsillectomy hemorrhage must be evaluated in the context of primary (bleeding in the first 24 hours after tonsillectomy due to inadequate hemostatic technique) vs secondary (bleeding occurring more than 24 hours following tonsillectomy) bleeding.<sup>25</sup> In our study, there were 4 primary bleeding events, 2 in each group. When reporting postoperative hemorrhage,

stratification of postoperative bleeding into primary and secondary events and the severity of bleeding should be characterized. Reporting of bleeding severity has not been standardized, complicating the interpretation of many studies of posttonsillectomy bleeding. By stratifying bleeding severity (Box), we could place more emphasis on level II and III bleeding events because they

**Table 2.** Bleeding Event Rate of the Intention-to-Treat and Per-Protocol Analyses<sup>a</sup>

Bleeding Event	No./Total No. (%) of Patients		% Difference (Upper Limit 97.5% CI)	Noninferiority P Value
	Dexamethasone	Saline		
Intention-to-treat analysis				
Level I	11/157 (7.0)	7/157 (4.5)	2.6 (7.7)	.17
Level II	3/157 (1.9)	5/157 (3.2)	-1.3 (2.2)	<.001
Level III	3/157 (1.9)	1/157 (0.6)	1.3 (3.8)	.002
Per-protocol analysis				
Level I	11/154 (7.1)	7/151 (4.6)	2.5 (7.8)	.18
Level II	3/154 (2.0)	5/151 (3.3)	-1.4 (2.2)	<.001
Level III	3/154 (2.0)	1/151 (0.7)	1.3 (3.8)	.002

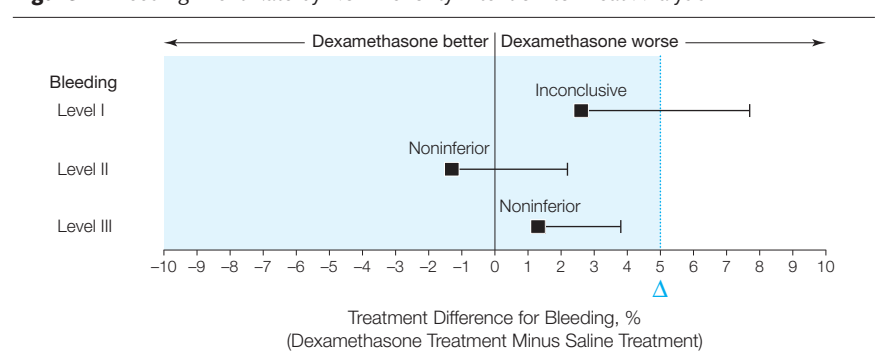
<sup>a</sup>Six patients who were lost to follow-up and 3 patients who received postoperative corticosteroids were excluded from the per-protocol analysis. Level I bleeding event indicates self-reported or parent-reported postoperative bleeding; level II bleeding event, required inpatient admission for postoperative bleeding; and level III bleeding event, required reoperation to control postoperative bleeding.

**Table 3.** Bleeding Event Rate of Per-Protocol Analysis Excluding Primary Bleeding Events<sup>a</sup>

Bleeding Event	No. (%) of Patients		% Difference (1-Sided 97.5% CI)	Noninferiority P Value
	Dexamethasone (n = 154)	Saline (n = 151)		
Level I	11 (7.1)	7 (4.6)	2.5 (0-7.8)	.18
Level II	2 (1.3)	3 (2.0)	-0.7 (0-2.2)	<.001
Level III	2 (1.3)	1 (0.7)	0.6 (0-2.8)	<.001

<sup>a</sup>Level I bleeding event indicates self-reported or parent-reported postoperative bleeding; level II bleeding event, required inpatient admission for postoperative bleeding; and level III bleeding event, required reoperation to control postoperative bleeding.

**Figure 2.** Bleeding Event Rate by Noninferiority Intention-to-Treat Analysis



Error bars indicate 1-sided 97.5% CIs. Tinted area indicates zone of inferiority. The noninferiority margin was set at 5%, meaning a difference in bleeding rates that did not exceed 5% would be taken as evidence that the bleeding with dexamethasone is not greater than that with placebo by more than 5%. Level I bleeding event indicates self-reported or parent-reported postoperative bleeding; level II bleeding event, required inpatient admission for postoperative bleeding; and level III bleeding event, required reoperation to control postoperative bleeding.

were more objective than level I (self-reported) bleeding and are associated with greater risk to patients. Although we counseled all of our parents to report any bleeding event, many patients with level I bleeding events were nondescript and self-limited. In the majority of these cases, parents did not report bleeding events until the follow-up appointment, and then only when prompted by the questionnaire. This was explained by the minor or questionable nature of these bleeding events. Some examples included a "warm sensation in the mouth" or a "bloodstain on a pillow case." The level II and III postoperative bleeding events are a more reliable indicator for complications because they are documented by treating physicians. These events are also associated with substantial morbidity and cost that occurs with prolonged hospitalization and the need for reoperations.

An inappropriately selected, noninferiority margin can result in an improperly powered study. We used level II and III bleeding events to establish our study size because these events are more objective and clinically important than level I bleeding events. We used our institutions' outcomes data for level II and II bleeding events coupled with published literature reports to determine the noninferiority margin of 5% for our study. We were limited in this approach because most published studies did not report bleeding severity. Other potential limitations include the use of multiple surgeons and institutions. Standardization of procedures should have minimized the effect of this potential limitation. We did not stratify dosing of dexamethasone. We only used a single, routinely used dose that was commonly cited in the literature. Graded dexamethasone doses would have required a much larger sample size, diminishing the feasibility of completing this study.

In conclusion, in this prospective, randomized study of 314 children undergoing tonsillectomy, perioperative dexamethasone administration was not associated with more level II or III

bleeding events than placebo as shown by noninferiority. Increased subjective (level I) bleeding events caused by dexamethasone could not be excluded because the noninferiority threshold of 5% was crossed.

**Author Contributions:** Drs Gallagher and Hartnick had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Gallagher, Ference, Keamy, Hartnick.

**Acquisition of data:** Gallagher, Hill, Ojha, Keamy, Williams, Hansen, Collins, Setlur, Capra, Brigger, Hartnick.

**Analysis and interpretation of data:** Gallagher, Hill, Ojha, Maurer, Brigger.

**Drafting of the manuscript:** Gallagher, Ference, Collins, Setlur, Hartnick.

**Critical revision of the manuscript for important intellectual content:** Gallagher, Hill, Ojha, Ference, Keamy, Williams, Hansen, Maurer, Setlur, Capra, Brigger, Hartnick.

**Statistical analysis:** Ference, Maurer, Brigger, Hartnick.

**Administrative, technical, or material support:** Gallagher, Hill, Ference, Collins, Setlur, Capra.

**Study supervision:** Gallagher, Keamy, Brigger, Hartnick.

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**Online-Only Material:** eMethods is available at <http://www.jama.com>.

**Additional Contributions:** Michael Cunningham, MD (Boston Children's Hospital, Boston, Massachusetts), and Donna Neuberger, PhD (Harvard School of Public Health, Boston, Massachusetts), provided comments on the analysis of the manuscript; James Ware, PhD (Harvard School of Public Health, Boston, Massachusetts), provided comments on the design of the manuscript; and Christine Finn, PhD (Massachusetts Eye and Ear Infirmary, Boston, Massachusetts), Cheryl McNeal (Naval Medical Center, San Diego, California), Vanessa DeGuzman (Massachusetts Eye and Ear Infirmary, Boston, Massachusetts), and David Baxter (Harvard Vanguard Associates, Boston, Massachusetts) helped with the acquisition of data. Drs Cunningham, Ware, and Neuberger received no compensation and Dr Finn, Ms McNeal, Ms DeGuzman, and Mr Baxter were all compensated for their contributions.

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