Postoperative Ibuprofen and the Risk of Bleeding after Tonsillectomy with or without Adenoidectomy

Analysis Plan

Prepared by:

Gillian Diercks, M.D.

Rie Maurer, M.S.

May 1, 2012

Introduction

This document summarizes the statistical analysis plan for the study entitled "Postoperative Ibuprofen and the Risk of Bleeding after Tonsillectomy with or without Adenoidectomy".

Study design

This study is a randomized, two-arm, blinded, non-inferiority study to evaluate the effects of ibuprofen on postoperative bleeding and pain. Consented and eligible subjects will be randomized to receive either ibuprofen (treatment arm) or acetaminophen (control arm) postoperatively. Eligible subjects are children aged 2-18 years undergoing tonsillectomy with or without adenoidectomy with electrocautery for recurrent tonsillitis and sleep disordered breathing/obstructive sleep apnea (OSA). Children with the following characteristics will be excluded from participation in the study: NSAID or aspirin allergy, acetaminophen allergy, bleeding disorders, asthma, lung, kidney or liver disease, or allergy to the dyes used in the medications.

The primary objective of this study is to determine if postoperative ibuprofen at 10mg/kg dosing QID (for times daily, roughly Q6 hours) postoperatively for 9 days is associated with an increased rate of post-tonsillectomy bleeding requiring operative intervention for hemostasis (type 3 bleeding) in children when compared with acetaminophen at 15mg/kg dosing QID. Secondary outcomes include comparing rates of post-tonsillectomy hemorrhage based on patient age, indication for tonsillectomy, and operating surgeon, as well as evaluating the effectiveness of ibuprofen as a post-tonsillectomy analgesic.

This is a non-inferiority study which seeks to demonstrate that post-operative ibuprofen is not associated with a clinically significant increase in postoperative bleeding rate, compared with acetaminophen, in children undergoing tonsillectomy. The null hypothesis for the primary aim is inferiority of ibuprofen; that is, subjects randomized to receive ibuprofen postoperatively after tonsillectomy will have an increased rate of post-tonsillectomy hemorrhage requiring operative intervention (type 3 bleeding) compared with subjects receiving acetaminophen. The alternative hypothesis is that bleeding rate with ibuprofen is not greater than acetaminophen by more than the non-inferiority margin. This non-inferiority margin was set at 3%.

The overall sample size of 722 (361 per study arm) for the primary analysis was calculated using a group sequential two proportions non-inferiority method using East V5.4.2 and O'Brien –Flemming stopping boundaries determined by means of the Lan-DeMets approach with the following parameters: one sided alpha of 0.025, power of 80%, 5% projected loss to follow-up rate, acetaminophen (control) type 3 bleed rate of

2%, non-inferiority difference of 3%, and 3 anticipated looks at the data (14%, 50% and 100% enrollment).

Subjects will be recruited from the following five sites:
1. Massachusetts Eye and Ear Infirmary (MEEI), Boston, MA
2. Madigan Army Base, Tacoma, WA
3. Naval Medical Center, San Diego, CA
4. Naval Medical Center, Portsmouth, VA

Recruited subjects that are eligible will be offered to consent and randomized in a one-to-one scheme using a uniform (1, 2) random number generator (*www.randomizer.org*) in blocks. This is a double-blinded study. Both the patient/parent and the healthcare providers (surgeon and nurses) will be blinded to which arm the patient is randomized.

The surgical technique used in the tonsillectomy with or without adenoidectomy along with the pain management prior and during the surgery is prescribed by the protocol. Postoperative pain management is dependent on randomization. All subjects will be randomized prior to surgery.

Main Outcome Measure and Classification of Bleeding Events

Post-tonsillectomy bleeding is the main outcome measure. This is categorized into type 1, type 2, and type 3 bleeding based on severity as well as time of bleeding, as determined by a physician-conducted postoperative bleeding questionnaire and review of written and electronic hospital records. These events will have two classifications:
1. Primary vs. Secondary (based on timing)
   a. ***Primary***: bleed occurs < 24 hours after surgery
   b. ***Secondary***: bleed occurs >/= 24 hours after surgery
2. Levels 1-3 (based on severity)
   a. ***Level 1***: children with any history of postoperative bleeding, regardless of whether there was clinical evidence of bleeding upon medical evaluation. This level includes all children with a history of postoperative bleeding who presented for evaluation/treatment by a physician in the Emergency Department, inpatient unit or operating room.
   b. ***Level 2***: children who require inpatient admission for postoperative hemorrhage regardless of the need for operative intervention. This level of severity excludes children who were evaluated in the emergency room who had no clinical evidence of hemorrhage or clot and were deemed safe for discharge home without admission for observation or intervention.
   c. ***Level 3***: the highest level of severity, includes children who required hospital admission and return to the operating room for control of post-tonsillectomy hemorrhage. This is our main outcome measure.

The endpoint for the primary analysis is either 1.a. or 1.b. and only 2.c. above (i.e. all Level 3 primary or secondary tonsil bleeds). For those subjects with more than one distinct bleed event within the study follow-up period, the most severe event will be considered for the primary analysis.

Secondary Endpoint: Effectiveness

Effectiveness will be measured by self-reported pain control. See **Appendix I** for pain questionnaire (only the questionnaire from Day 0 is included as Days 1-8 are the same). The *primary* definition of effectiveness will be overall rating of the child's pain (mild, moderate, severe); *secondary* definitions will include the four categories for crying, excitement, anxiety and verbalization of pain (0, 1, 2; corresponding to no experience of this symptom, mild and moderate/severe).

Specific Aims

- *Primary Aim 1*: To compare the rates of post-tonsillectomy bleeding between pediatric patients who receive postoperative ibuprofen to those who receive acetaminophen in a prospective, randomized, blinded and controlled trial.
- *Secondary Aim 2*: To compare the rates of post-tonsillectomy hemorrhage when studying different groups of patients based upon their age, indication for tonsillectomy, or operating surgeon.
- *Secondary Aim 3*: To evaluate effectiveness of ibuprofen as a post-tonsillectomy analgesic in comparison to acetaminophen, which is currently the standard of care at our institution.

Statistical summaries and methods

All summaries and analyses will be presented overall and by study arm. There are two study arms: ibuprofen and acetaminophen.

Screening and eligibility

- Total # screened and reasons for ineligibility or reasons for refusal of consent (based on available data) will be presented in a CONSORT figure, along with some of the data in the sections that follow. A template for this figure from http://www.consort-statement.org/ is available in **Appendix II**.

Accrual

- Table: Randomization of subjects by month (or quarter?) by clinical center. Dates of first and last randomization.

- Figure: Either just a plot of # randomized on the y-axis and month+year on the x-axis OR a comparison of observed randomization with targeted randomization
- Describe any eligibility criteria violations. For example, a subject was randomized but consent was not in place or found to not meet a particular eligibility criterion after being randomized. Describe how these subjects were handled.
- Table: Number of subjects randomized by study arm by month+year and separately by clinical site.

Baseline characteristics and demographics

Baseline is defined as the last available value obtained on or before the day of randomization.

Table: summarize the following variables by study arm: *("Continuous statistics" will present: mean, standard deviation (SD), median, 10th and 90th percentiles, minimum and maximum values):*
- Sex: number (%) by sex
- Age: continuous statistics
- Indication for surgery: number (%) by recurrent tonsillitis, sleep disordered breathing, adenotonsillar hypertrophy, or other
- Surgery type: number (%) by tonsillectomy or tonsillectomy with adenoidectomy
- Surgeon performing operation: number (%) by surgeon number
- Study site: number (%) by the four sites
- Supplementary procedures: number (%) by procedure
- Prescribed narcotics postoperatively: number (%) prescribed

Completeness of Follow-up

Table: Number (%) by the following categories:
- Completed protocol-specified period of follow-up through 14 days postoperative
- Failure to complete follow-up, with reasons for loss to follow-up

Status of randomized treatment (ibuprofen/acetaminophen)

Table: Number (%) by the following categories:
- Completed assigned study treatment as prescribed by the protocol (with no missed doses)
- Completed assigned study treatment but missed some doses or temporary treatment interruptions (separate adherence issues from toxicity issues and summarize number of missed doses and reasons missed)

- Early discontinuation of study treatment (including reasons for premature discontinuation, including toxicity)

Adverse events (other than bleeding)

Table: Hematological abnormalities by test code and grade separately by study arm (only include events that are at least one grade higher than existing graded event at baseline)
Table: Diagnosis by category (as determined by principal investigator upon review of recorded diagnoses) and grade separately by study arm (only include events that are new or one grade higher than those existing at baseline)

Primary Objective

The primary analysis will be intent-to-treat (ITT). All randomized subjects will be included with the exception of any that withdrew consent or were found to be ineligible post-randomization (see **Study Design** section above) and did not receive the study medication. All other randomized subjects will be included.

This ITT primary analysis (*Aim 1*) will be a simple, univariable analysis to evaluate the association between ibuprofen and bleeding. As described above, the outcome will be type 3 bleeding (including both primary and secondary). The null hypothesis (the type 3 postoperative hemorrhage rate in subjects on the ibuprofen arm differed from the bleeding rate of subjects on the acetaminophen arm) will be rejected if the difference in bleeding rates do not exceed 3%, which is the preset non-inferiority margin, and the conclusion will be that the type 3 bleeding in the ibuprofen study arm is not greater than that in the acetaminophen arm by more than 3%. Thus, the hypotheses are as follows:

$$H_0: p_{ibuprofen} - p_{acetaminophen} \geq 0.03$$
$$H_a: p_{ibuprofen} - p_{acetaminophen} < 0.03$$

One-sided confidence intervals will be used to compare the difference in bleeding rate between the two study arms. This difference will be compared using a Wald test with an overall significance level of 0.025. Analysis will be performed for both primary and secondary bleeding.

Secondary Objectives

Secondarily, a multivariable logistic regression model (*Aim 2*) will assess this primary bleeding outcome with adjustment for pain control (primary definition of effectiveness as recorded on the day before the bleed event) and potential confounding variables (including study site, narcotics use, age, surgical indication, gender and operating

surgeon). A variable will be considered confounding with study arm if the parameter estimate for study arm changes by more than 10% once the potential confounder is included in the model. Any variables meeting this definition will be included in the adjusted model regardless of significance-level.

Both the univariable and multivariable analyses will include all randomized subjects and be intent-to-treat. This includes those that are lost to follow-up. Those that are lost to follow-up will be assumed to not have had a Type 3 bleed unless there is a hospital record of type 3 bleeding on chart review. Subjects considered to be lost to follow-up will be those who do not return for their postoperative visit.

The final protocol-specified secondary objective (*Aim 3*) is to evaluate the effectiveness of ibuprofen as a post-tonsillectomy analgesic in comparison to acetaminophen. Using the primary definition of effectiveness we will compare the experience of pain based on the overall category (mild, moderate or severe) and study treatment arm (mortrin versus acetaminophen) using ordinal logistic regression separately for each postoperative day. Subsequent regression models will be adjusted for study site, narcotics use, age, surgical indication, gender and operating surgeon. It is not of interest to assess changes in pain over time since post-tonsillectomy pain does not improve consistently in the first eight days post-surgery. For example, it is not unusual for a patient to have severe pain on postoperative (PO) days 0-3, improved pain levels on PO days 3-5 and then increased pain on PO days 5-8.

Additionally, assess the correspondence between the primary definition of effectiveness and the secondary definitions (crying, excitement, anxiety and verbalization of pain). Tables will summarize overall primary pain response by the each of the four secondary definitions, separately for each of the 9 days that this data was collected. The Mantel-Haenszel test will be used to assess whether the primary and secondary definitions increase or decrease in similar ways (since are measures of pain are ordinal and we are interested in the linear association between these two measures).

Appendix I: Medication Dosing Schedule and Pain Scale Questionnaire

Patient Name: _____

Date of Surgery: _____

MEDICATION DOSING AND PAIN SCALE INSTRUCTIONS

As part of your participation in our study investigating the use of ibuprofen after tonsillectomy, please complete the following pain scale daily each evening. This packet contains 9 scales. The first should be completed today- the date of surgery- and the other scales should be completed on postoperative day 1 through 8, for a total of 9 days.

If your child was also prescribed oxycodone and received that medication, please indicate this on the questionnaire corresponding to the day during which it was given.

Please bring your completed questionnaires, as well as any remaining study medication, to your postoperative visit for collection and review.

Patient Name: _____

POSTOPERATIVE DAY 0 (DAY OF SURGERY) MEDICATION DOSING AND PAIN SCALE

Please place a check in the appropriate box each time you give your child a dose of the study medication.

	DOSE 1	**DOSE 2**	**DOSE 3**	**DOSE 4**
Check the box if medication was given				

If your child is eligible to receive oxycodone, was this given today? (circle response)
Yes   No

Directions: For each item, please circle the number that best corresponds to your child's behavior.

Crying?	No	0
	Yes but response to TLC*	1
	Yes but does not respond to TLC*	2
Excitement	None	0
	Restless	1
	Thrashing	2
Anxiety	Asleep	0
	Mild	1
	Hysterical	2
Verbalization of pain	Asleep/states no pain	0
	Cannot localize pain	1
	Can localize pain	2

* TLC = tender loving care

Directions: Please rate your child's pain as mild, moderate, or severe based on the descriptions noted below.

Rate your child's pain:	
Able to tolerate soft diet, slept for 8-10 hours per night	Mild
Difficulty tolerating a soft diet, awoke once or twice in 8-10 hour night complaining of pain	Moderate
Could not tolerate a soft diet, tolerates liquid diet at best; awoke several times over 8-10 hour night because of pain and discomfort	Severe

Appendix II

C O N S O R T
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

Enrollment

Assessed for eligibility (n=)

Excluded (n=   )
♦ Not meeting inclusion criteria (n=   )
♦ Declined to participate (n=   )
♦ Other reasons (n=   )

Randomized (n=)

Allocation

Allocated to intervention (n=)
♦ Received allocated intervention (n=)
♦ Did not receive allocated intervention (give reasons) (n=)

Allocated to intervention (n=)
♦ Received allocated intervention (n=)
♦ Did not receive allocated intervention (give reasons) (n=)

Follow-Up

Lost to follow-up (give reasons) (n=)

Discontinued intervention (give reasons) (n=)

Lost to follow-up (give reasons) (n=)

Discontinued intervention (give reasons) (n=)

Analysis

Analysed (n=)
♦ Excluded from analysis (give reasons) (n=)

Analysed (n=)
♦ Excluded from analysis (give reasons) (n=)