Study Protocol

Title: Ketorolac as a Strategy for Reducing Post-operative Opioid Requirements in Children with Obstructive Sleep Apnea Undergoing Adenotonsillectomy: a Randomized Controlled Trial

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REVISION HISTORY

No need to review this section if this is the first version of the protocol you are submitting to the IRB

Revision #	**Version Date**	**Summary of Changes**
1	20APR22	New protocol template.
2	20APR22	Statement to include Ketorolac is not indicated for use in the pediatric population. (Section 5)

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1. Study Summary

Project Title	Ketorolac as a Strategy for Reducing Post-Operative Opioid Requirement in Children with OSA undergoing Adenotonsillectomy: A Randomized Contolled Trial
Project Design	This study is designed as a randomized controlled trial with participants assigned to either Ketorolac or Morphine.
Primary Objective	Determine the effect of Ketorolac administration on total postoperative Morphine dosage required to achieve analgesia in children
Secondary Objective(s)	Characterize the effect of intra-operative ketorolac administration on FLACC pain scores and PACU recovery time
Research Intervention(s)/Interactions	Ketorolac or Morphine for post-operative
Study Population	Children's Healthcare of Atlanta- Egleston
Sample Size	120
Study Duration for individual participants	One Day
Study Specific Abbreviations/ Definitions	OSA: Obstructive Sleep Apnea
Funding Source (if any)	Department: Atlanta Gas Light funds

2. Objectives

Our primary aim is to determine the effect of ketorolac administration on total postoperative morphine dosage required to achieve analgesia in children with OSA undergoing adenotonsillectomy. Our secondary aim will be to characterize the effect of intra-operative ketorolac administration on FLACC pain scores and PACU recovery time. The measures we will monitoring are PACU morphine requirements, FLACC pain scores, PACU recovery time, incidence of post-tonsillectomy bleeding and total amount of pain medications administered during hospitalization.

3. Background

Obstructive sleep apnea (OSA) as an indication for adenotonsillectomy has increased significantly over the past ten years, and now has surpassed recurrent tonsillitis as the most

common indication for this procedure[1]. Opioids continue to be the most commonly administered pain medication for these procedures. Studies have shown that patients with OSA have significantly increased sensitivity to opioids that results in post-operative respiratory depression and apnea when administered via standard opioid dosing protocols[1-3]. Children with OSA were shown to have a nearly fivefold increase in the odds of developing respiratory complications when compared to their counterparts with tonsillitis[4]. As such, it is imperative that current anesthetic management of children undergoing this procedure remains as safe and effective as possible for this growing population. Ketorolac possesses similar efficacy to morphine without the same incidence of respiratory depression, nausea and vomiting, which are commonly seen post-adenotonsillectomy[5]. Importantly, when combined with opioids, ketorolac is opioid-sparing. This synergistic effect means that a similar level of analgesia is achieved using a lower dose of opioid. However, there continues to be concern about using ketorolac due to the potential risk of post-operative bleeding from anti-platelet activity.

To our knowledge, the use of ketorolac as part of an analgesic regimen has not yet been studied in the specific population of children with OSA undergoing adenotonsillectomy, though they stand to benefit from it the most. In this randomized prospective study, we will determine the effect of ketorolac on the total dose of morphine required to achieve postoperative analgesia in children with OSA undergoing adenotonsillectomy.

4. Study Endpoints

We hypothesize that by administering ketorolac at the end of the procedure once hemostasis has been achieved, we can decrease the amount of morphine administered in the PACU. By decreasing FLACC pain scores and opioid administration, we aim to decrease the PACU length of stay. Additional costs are incurred due to utilization of additional resources, increased length of stay, and unanticipated intensive care. This study will provide a more comprehensive understanding of the efficacy and safety of the current standard postoperative analgesic regimen employed at our institution, in which opioid analgesia currently plays a prominent role.

5. Study Intervention/Investigational Agent

Although not indicated for use in the pediatric population, Ketorolac possesses similar efficacy to morphine and other major opioid analgesics, but does not cause respiratory depression and is not associated with nausea and vomiting, both commonly described complications post-adenotonsillectomy[5]. Importantly, when combined with opioids, it is opioid-sparing. This synergistic effect means that a similar level of analgesia is achieved using a lower dose of opioid. Improved quality of analgesia, in addition to reduction of opioid-related adverse effects, makes ketorolac an ideal adjuvant to study in an OSA population. While data remain mixed as to whether ketorolac contributes to increased hemorrhage post-adenotonsillectomy through

inhibition of platelet aggregation and prolonged bleeding time, several studies have recently emerged that are either reassuring or equivocal.

A systematic review and meta-analysis showed that while ketorolac is associated with a five-fold bleeding risk in adults after any surgical procedure, children under 18 were not at a significantly increased risk for bleeding post-tonsillectomy[5]. Another quantitative systematic

review showed that while NSAIDs were equianalgesic when compared with opioids, and the risk of emesis was significantly decreased, the evidence for NSAIDs to increase bleeding risk post-tonsillectomy was equivocal[9]. A recently updated Cochrane study reviewed 15 trials assessing the effect of NSAIDs on bleeding in children undergoing elective tonsillectomy or adenotonsillectomy[8], which found no significant increased risk of bleeding when NSAIDs are used in pediatric tonsillectomy.

6. Procedures Involved

After consent has been obtained, patients will be randomly assigned to ketorolac group or non-ketorolac group. All patients will receive a similar anesthetic with inhalational induction with the exception of the ketorolac group receiving 0.5mg/kg IV ketorolac at the end of the procedure once hemostasis has been achieved. The PACU nurses, who will be blinded to ketorolac administration, will evaluate the patients using FLACC scores at 10 minutes post-op, 20 minutes post-op and at time of PACU discharge. For patients with a FLACC score of 6-10, morphine 0.05mg/kg will be administered. For patients with FLACC scores of 3-5, morphine 0.025mg/kg will be administered. The total amount of opioid required to obtain a FLACC score of less than 3 will be evaluated as the primary outcome. The secondary outcomes to be evaluated will be PACU FLACC scores, time required in PACU, incidence of post-tonsillectomy bleeding and total pain medications administered during hospital admission.

All patients will undergo inhalational induction with Nitrous Oxide and Sevoflurane. After IV placement, propofol 1-3mg/kg and fentanyl 1mcg/kg will be administered prior to intubation. Immediately after induction, dexamethasone 0.5mg/kg and an IV infusion of acetaminophen 15mg/kg will be administered. During the intra-op course, dexmedetomidine 0.5mcg/kg and odansetron 0.1mg/kg will be given. Patients in the ketorolac group will receive 0.5mg/kg IV, while those in the non-ketorolac group will not receive any.
A rescue dose of Fentanyl 0.5-1mcg/kg IV will be available for administration at the end of the procedure. The decision to administer this will be left to the discretion of the attending anesthesiologist for the case. The choice to give this will be made based on variables including patient's condition and a 20% increase in the heart rate and blood pressure.In PACU, nurses will be blinded to ketorolac administration, but will be informed of all other medications given.

The PACU nurses will evaluate the patients using FLACC scores at 10 minutes post-op, 20 minutes post-op and at time of PACU discharge. For patients with a FLACC score of 6-10, morphine 0.05mg/kg will be administered. For patients with FLACC scores of 3-5, morphine 0.025mg/kg will be administered. For patients with FLACC scores of 0-2, no morphine will be administered. The total amount of morphine required to obtain a FLACC score of less than 3 will be recorded.

The PACU length of stay will be monitored as a secondary outcome, as decreasing the PACU length of stay may also be a benefit of ketorolac administration. In addition, we will monitor for post-tonsillectomy bleeding and categorize as either post-tonsillectomy bleeding requiring surgical intervention or post-tonsillectomy bleeding not requiring surgical intervention. In addition, the total amount of pain medication required during hospitalization will be evaluated. Once the patient is discharged, there will be no further collection of data or follow-up with the participant.

7. Statistical Analysis Plan

Descriptive statistics will be calculated for all variables of interest and will include means and standard deviations, medians and ranges, or counts and percentages, as appropriate. Characteristics of subjects who received ketorolac will be compared to those who did not receive ketorolac using Chi-square tests for comparisons of categorical variables (i.e. gender, race, etc.) and two-sample tests or Mann-Whitney tests for continuous variables (i.e. age, apnea hypopnea index, etc.). For binary outcomes, such as post-tonsillectomy bleeding, cohorts will be compared using Chi-square tests. Generalized linear models will be used to compare differences in amount of narcotic among the two tonsillectomy cohorts, adjusting for any differences in patient and surgical characteristics that may exist between the two groups. Statistical significant will be performed using Stata v. 13.1 (College Station, TX).

8. Sharing of Results with Participants

Study results will not be shared with participants.

9. Study Timelines

- The duration of an individual participant's participation in the study.
- The duration anticipated enrolling all study participants.
- The estimated date for the investigators to complete this study (complete primary analyses)

The subject will participate for one day.

10. Inclusion and Exclusion Criteria

Inclusion Criteria:

- Patients 2 years old through 18 years of age
- Diagnosis of sleep disordered breathing or obstructive sleep apnea
- Children undergoing elective tonsillectomy or adneotonsillectomy at Children's Healthcare of Atlanta Egleston location
- Parent or legal guardian willing to participate, and able to understand and sign the provided informed consent
- No known coagulation defect

Exclusion Criteria:

- Parent or legal guardian unwilling to participate or understand and sign the provided informed consent
- Known coagulation defect
- Patients on longstanding NSAID therapy
- Known renal impairment

11. Vulnerable Populations

Females that are pregnant or believe to be pregnant, will not be considered for participation in the study, due to medical contraindications.
Cognitively Impaired children will not be considered for participation in the study.

12. Local Number of Participants

We will enroll a total of 120 participants for this study.

13. Recruitment Methods

- Both the Principal Investigator and study staff will take initiative to search for potential study candidates on Epic.
- Potential patients will be identified on Epic via surgery status board. Patients who are undergoing adenotonsillectomy will be approached by study staff prior to their procedure.
- No flyers, advertisements or social media/online recruitment mechanisms will be used to recruit patients.

14. Withdrawal of Participants

Parents or Legal Authorized Representative may withdrawal participant from study without penalty at any given time.
A participant may be withdrawn from study if their surgery is scheduled after hours, or if they do not receive paralytic.
Principal Investigator may withdrawal subject at her discretion as deemed fit for patient safety.

15. Risk to Participants

The drug that is being tested may not work any better than regular care. 1-10% of patients that take Ketorolac may have:

- Nausea
- Abdominal Pain
- Headaches

Serious, less common risks include:

- Post-procedure bleeding, after tonsil removal (3%), in children with OSA (2%)
- Less than (1%): chance of allergic or anaphylactic reaction.

16. Potential Benefits to Participants

The study drug may not work any better than regular care; however, we anticipate less morphine will be administered post-operatively.

17. Compensation to Participants

There will be no compensation provided to participants.

18. Data Management and Confidentiality

Confidentiality will be maintained throughout the entire process from obtaining consent to data analysis. Confidentiality will be maintained by only recording information absolutely necessary to fulfill the study's objectives. Information directly identifying patients (names, addresses, telephone numbers, social security numbers, email addresses, and account numbers) will be excluded from any publication or presentation. In the research database, patients will be identified by their assigned study number. The database, along with the code linking a subject's identity to an assigned number, will be locked in the office of the principal investigator or designee.

If a participant declines to participate in the study, the participant will not be assigned a study ID number and the study coordinators will not collect any data on the participant. If the participant agrees to participate in the study, the participant will be assigned a study ID number and the study coordinators will collect data points pertinent to the study. These procedures will help prevent unauthorized inclusion of the patient's data in the RedCap database.

19. Provisions to Monitor the Data to Ensure the Safety of Participants

Monitoring of Adverse Events (AEs) and Serious Adverse Events (SAEs) is an important aspect of data collection. After enrollment, the principal investigator or designee will collect the adverse experiences from the medical record. The study subjects will be reviewed on a case-by-case basis. The principal investigator will determine the seriousness of each adverse event and

whether or not the event was related to the study. Serious adverse events (life-threatening, requiring intervention) will be reported to the IRB within the guidelines set by the IRB.

After 50% of patients enrolled have undergone surgery, evaluation of the rates of post-tonsillectomy bleeding will be carefully evaluated. If any significant increase is noted, the study will be evaluated by the principal investigator for possible discontinuation.

20. Provisions to Protect the Privacy Interest of Participants

Potential participants will be approached for consent in a private area/room to discuss study procedures. Participants will have ample time to ask any questions during consent process; they will be reminded that their participation in the study is voluntary, and they will not be penalized if they choose not to participate in the study. Participant discussion and data will be limited to study personnel only.

21. Economic Burden to Participants

Participants will not incur any charges related to the study.

22. Informed Consent

Only those patients who meet the Inclusion criteria will be considered as possible study candidates. A thorough discussion between the parents or legal guardian and the principal investigator, or the study coordinator will occur during the study consent process. No study related procedure will occur prior to obtaining appropriate informed consent. Patients will be enrolled consecutively as they present to Children's Healthcare of Atlanta. The parents or legal guardian of the patient will be approached in clinic prior to surgery by the principal investigator, or the study coordinator to discuss the goals, benefits and risks of the project. Written informed consent will be obtained following this discussion. For the occasions when parents do not arrive at the hospital until the day of surgery, they will be approached only if there is sufficient time to allow for their full consideration. One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

Patients undergoing emergent/urgent procedures or when there is insufficient time for the parents to thoroughly consider the goals, benefits and risks of this project will not be approached for enrollment.

Non-English-Speaking Participants

Due to budget restrictions, we will not approach Non-English speaking candidates.

Cognitively Impaired Adults

Adults who are cognitively impaired will not be approached for study enrollment.

23. Setting

- The research team will identify patients at Children's Healthcare of Atlanta-Egleston, that meet the inclusion criteria via Epic by viewing surgery status board.

- Potential candidates will be approached
- The CHOA pharmacy will dispense the study drug after the patient is ramdomized.
- The study drug will be administered in the operating room, the patient will be followed in the PACU for collection of study data points.
- Once the patient has been discharged from the hospital, there will be no follow-up by the study team and no additional data will be collected.

24. Resources Available

All study staff have completed the required CITI training and understand their duties and role in the study. Knowledge of the protocol and study procedures will be reviewed with study members prior to patient recruitment; this will ensure patients are screened, consented, and monitored appropriately.

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