TITLE: Does Montelukast decrease post Adenotonsillectomy pain in children? A Randomized Controlled Trial.

STUDY ID: 2015-8935

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ABSTRACT

Objective: The purpose of the present study is to evaluate the effectiveness of perioperative Montelukast as an analgesic for adenotonsillectomy

Study Design: Randomized controlled double blinded clinical trial.

Setting: Cincinnati Children's Hospital Medical Center (CCHMC), Division of Pediatric Otolaryngology, Head and Neck Surgery

Methods: Children between the age of 3-8 undergoing adenotonsillectomy with planned 23 hour observation for adenotonsillar hypertrophy and sleep disordered breathing will be randomized to receive either montelukast or placebo in Same Day surgery and post-operatively.

Analysis: Differences in demographics (age, gender, race, weight) between the intervention and control groups will be assessed using chi-square (for categorical measures) and t tests (for continuous measures). Differences in postoperative opioid usage, postoperative pain scores using the FLACC scale, and the number of postoperative contacts (Emergency department visits or phone calls) with patients or their family regarding pain or tonsillar hemorrhage will be evaluated using chi-square (categorical measures) and t tests (continuous measures).

PURPOSE OF STUDY

Adenotonsillectomy (T&A) is the one of the most common pediatric procedures performed in the United States, with over 530,000 procedures performed annually[1]. Pain control after T&A is essential for improving recovery and enhancing quality of life. At CCHMC, our current protocol in patients over the age of three is to treat pain with scheduled Tylenol, ibuprofen and steroids, as well as opioids (oxycodone) as a "rescue" medication for uncontrolled pain. Despite this regimented approach, pain control is often suboptimal, and numerous doses of opioids are often required. Montelukast is a cysteinyl leukotriene receptor antagonist that may have a role in decreasing post T&A pain[2]. The primary objective of the present study is to evaluate the effect of montelukast on post-T&A pain by measuring the amount of opioid pain medication required postoperatively in patients receiving montelukast perioperatively compared to those receiving placebo. The secondary objective will evaluate post-surgical outcomes and include group comparisons of post T&A pain scores and number of Emergency department visits and/or phone calls for perioperative pain related complaints.

Hypothesis #1

Perioperative montelukast will decrease the amount of opioid pain mediation required in the first 24 hours postoperatively compared to those in the control group.

Hypothesis #2

Perioperative montelukast will decrease pain scores in the first 24 hours after surgery in patients undergoing T&A compared to those in the control group.

Hypothesis#3
Perioperative montelukast will decrease the number of postoperative contacts (Emergency department visits and phone calls) by parents for pain related concerns in the first 3-4 weeks after surgery.

Hypothesis#4
Response to montelukast as a pain medication may differ based on different single nucleotide polymorphisms (SNP's) in the study population.

BACKGROUND:
Over 2000 T&A's are performed at CCHMC each year, making it the second most common surgical procedure performed at CCHMC after myringotomy and tube placement. Pain is a well-known sequelae of tonsillectomy and adenoidectomy (T&A), and treatment of this pain has an important role in improving recovery and enhancing quality of life in a pediatric population[3]. Post-tonsillectomy pain is commonly treated with a multimodal approach, usually with some combination of acetaminophen, NSAIDs and opioid pain medication[4-6]. Opioids are effective at controlling pain, but due to side effects such as respiratory depression, concern has been cast on the use of opioid medications in a pediatric population[7]. Due to this, other adjunctive pharmacologic treatments, including steroids and sucralfate, for post tonsillectomy pain have been considered[8, 9]. Technique has also been considered as a variable in post-tonsillectomy pain, with coblation and intracapsular techniques thought to decrease pain postoperatively[10, 11]. Despite numerous attempts to improve the process, tonsillectomy often remains a traumatic experience for both children and their parents.

Leukotrienes are bronchoconstrictors and pro-inflammatory molecules derived from the arachidonic acid 5-lipoxygenase pathway. They have long been known to play a role in bronchoconstriction (such as in asthma), and also play a role in attracting inflammatory cells to an area of injury[12]. Montelukast is a commonly used cysteinyl leukotriene receptor antagonist that modifies the 5-lipoxygenase pathway. Animal models suggest that modification of this process may attenuate pain, and trials in women with dysmenorrheal suggest that modification of this pathway may improve dysmenorrhea[13, 14]. Whole blood draws allow for examination of the plasma left after processing the sample. Through the collection and analysis of the plasma, it is possible to investigate these inflammatory biomarkers[12]. It may also have a role in decreasing post T&A pain[2]. It has been extensively studied in asthma and allergy[15] and allergic rhinitis[16], and is known to be safe for use in children[17]. It has the added benefit of being relatively familiar to otolaryngologists, who use it for rhinitis, and occasionally for children with obstructive sleep apnea[18]. Of note, the FDA recommends counseling patients who take montelukast, as there is concern that patients receiving daily montelukast have a higher risk of neuropsychiatric events[19]. However, evidence about a causal link between montelukast and psychiatric disorders is limited, as most patients receiving montelukast do so for asthma, which is known to predispose to a higher risk of psychiatric symptoms independent of montelukast[20]. The most neuropsychiatric symptom in a pre-teen pediatric

population is sleep disturbance. In patients who develop neuropsychiatric symptoms, these are generally thought to resolve after cessation of the medication[21-23].

Quantifying the amount of pain present postoperatively generally requires patient cooperation to rate pain. This is often difficult in a pediatric population, especially in the setting of emergence delirium in the PACU. The FLACC pain scale is a validated behavioral scale that is useful in pediatric patients up to the age of 16 who cannot or will not verbalize the severity of their pain, and measures both pain and psychologic distress[24-27]. At Cincinnati Children's Hospital, the FLACC scale is used by nursing staff to objectively quantify pain scores determine whether rescue narcotics are needed postoperatively. Previous research in CCHMC's T&A population suggests that the FLACC is a valid way of assessing post T&A pain (unpublished data).

Determining the amount of opioid medication taken by patients in the postoperative time is a way of determining the amount of pain experienced postoperatively. Due to concern about opioid medications and respiratory depression, interventions that decrease the amount of opioid pain medications taken are highly attractive[28]. Our study seeks to quantify the amount of opioid medication taken with and without adjunctive treatment with montelukast to determine if adequate analgesia can be obtained in the absence of opioid medications.

Finally, Montelukast is known to have a variable response based on different genotypes with respect to treatment in asthmatics (28-32). Previous studies have shown a highly variable response, with certain genotypes expressing a high degree of response to montelukast (28). Recent studies have identified 25-30 single nucleotide polymorphisms (SNP) that contribute to response to the drug, with a number of particular SNP's expressing a particularly high response rate (28, 32). Our goal is to run a pilot study using a similar analysis of loci previously identified in these genome wide studies to evaluate associations between polymorphisms in the 5-LO biosynthetic pathway to clinical effect to Montelukast

STUDY DESIGN: This is a prospective, randomized, double blinded study of patients undergoing adenotonsillectomy for the indication of adenotonsillar hypertrophy that is scheduled for overnight observation at CCHMC. Patients will be randomly assigned to either the control (Group 1) or treatment group (Group 2) at the time the procedure is scheduled. The order of assignment to groups will be determined by random number generator programmed by the project biostatistician. Patients will be stratified into groups by age: 1) 3-5 years of age 2) 6-8 years of age on a 1:1 basis. This leads to a total goal of 30 patients age 3-5 in group 1, 30 patients age 6-8 in group 1, with identical numbers in group 2 from each age cohort. The patients in Group 1 will be given a placebo medication (prepared by the CCHMC investigational pharmacy) in same day surgery 0-3 hours prior to planned surgery on the day of surgery by the anesthesia service. The patients in Group 2 will be given an age appropriate dose of Montelukast (prepared by the CCHMC investigational pharmacy) in same day surgery 0-3 hours prior to planned surgery on the day of surgery by the anesthesia service. T&A will be performed in the standard fashion with electrocautery in all patients. A suggested anesthesia protocol will be recommended to the anesthesia staff for surgery, but the final plan will be left to the discretion of the attending anesthesia provider. The total intraoperative morphine equivalent doses given will be recorded for analysis. Upon arrival to the PACU, pain will be treated with a standard protocol using the FLACC pain scale (a behavioral 0-10 pain scale validated for

use in pediatric patients). Patients will be treated with opioid rescue medications per nursing based on the FLACC scores (0-3= mild, no opioid given, 4-6= moderate, low dose opioid given, 7-10 = severe, high dose opioid given). Pain will be measured at 10, 40, and 80 minutes after surgery in the PACU, per standard protocol. A second dose of Montelukast or placebo will be given to the patient 9-13 hours post-operatively. Patients will then be admitted for overnight observation to the floor per standard protocol. Pain will be measured per current protocol on the floor using the FLACC scale, and opioid medication given as necessary. Standard demographic data, intra-op and post-operative data will be recorded along opioid usage, PACU and floor pain scores, post tonsillectomy hemorrhage rates, and rates of postoperative contacts (Emergency department visits or phone calls) for pain related concerns. The rate of postoperative contacts and post-tonsillectomy hemorrhage will be recorded on a postoperative phone call to the parents of patients undergoing adenotonsillectomy that is routinely carried out by CCHMC Otolaryngology nursing staff three weeks after surgery.

Blood analysis will be carried out with the assistance of the human genetics (division of molecular genetics) service. Samples will be evaluated for the 30 most common polymorphisms found to have influence on response to montelukast in previous studies, with a focus on genes coding for polymorphisms found to have influence on asthma treatment response (28-32). Relationships between different genotypes and the outcome variables (Visits to emergency department for pain, phone calls for pain, and pain scores) will be evaluated using correlation analysis and the appropriate statistical tests of difference (ANOVA). Baseline values for pain variables (opioids used, FLACC pain scores) will be obtained from the randomized trial numbers, and comparisons will be performed based on this data. Any polymorphisms found to have a significant impact on outcome in patients treated with montelukast will be analyzed against patients treated with placebo.

DATA ELEMENTS:

Pain medication: The EPIC electronic medical record will be evaluated by study personnel after patient discharge from the hospital. The Medication Administration Record (MAR) will be examined for all doses of opioid pain medication given while in the hospital, including that given in the PACU. This data will be entered into a secure database. In addition, the amount of intraoperative narcotic (given in morphine equivalents) will be recorded for analysis.

FLACC scale: Measurements for pain on the FLACC scale are obtained on all patients routinely by CCHMC PACU and ward nursing staff at 10, 40 and 80 minutes postoperatively, and upon arrival to the floor. These scores are entered into the EPIC electronic medical record by nursing staff as part of their assessments. Study personnel will evaluate the patient's medical record to determine the FLACC scores at 10, 40 and 80 minutes postoperatively, as well as upon arrival and during the child's stay on the floor.

Post-op contact log: All records of patient calls to the ENT office are recorded in the EPIC electronic medical record. Study personnel will evaluate the EPIC medical record after the 3-4 week phone call has been performed to evaluate for any contact with physicians for pain related issues. In addition, all ED visits are recorded in the EMR, and these will be evaluated for 3-4 weeks after surgery. Finally, at the 3-4 week phone call, patients are

routinely asked about pain control and any visits to a physician for T&A related issues. This information is recorded in the EMR. Study personnel will evaluate for this as well.

DURATION:
Each participant will be in the study from the time of informed consent through the 30 day post-drug administration follow-up. Adverse events will be collected beginning at the time of study drug administration and continue through until the phone call 3-4 weeks after surgery. Medical information will be obtained through the electronic medical record to determine baseline medical conditions.

The duration of the study is determined by our power analysis below and is expected to run until approximately 120 patients are recruited (60 age 3-5, and 60 age 6-8). Previous audits of our institutional records reveal that approximately 40 observation tonsillectomies in the ages of 3-8 are performed at CCHMC each month, with over 95% of these for an indication of adenotonsillar hypertrophy. Of these, approximately 60% are in patients age 3-5, and 40% are in patients ages 6-8. Assuming an 80% rate of assent by parents, approximately 32 patients per month will be enrolled, for a total of 20 patients age 3-5, and 12 patients age 6-8. Given expected recruitment of 60 patients in each age arm, the expected time for accruement of patients age 3-5 is approximately 3-4 months for patients age 3-5, and 5-7 months for patients age 6-8. We will plan on a maximum 1 year time period for all data collection. Data analysis, presentations and publications will be completed within 1 year after study completion. Total time of study is 2 years.

SELECTION AND RECRUITMENT OF PARTICIPANTS
All patients between the age of 3-8 who are scheduled to undergo a tonsillectomy or a tonsillectomy and adenoidectomy for adenotonsillar hypertrophy that are scheduled for overnight observation at CCHMC main campus and who meet all inclusion/exclusion criteria will be recruited for entry into the study. Potential subjects and/or the parents/guardians of all potential participants will be informed of the study protocol, risks, and benefits by the investigator or designee.

Inclusion: All patients between the ages of 3-8 undergoing adenotonsillectomy for an indication of adenotonsillar hypertrophy who are scheduled for overnight observation at CCHMC main campus.

Exclusion criteria:
* Moderate-severe developmental delay
* Indication for chronic tonsillitis
* Allergies or contraindications to study medications
* Moderate to severe cardiac, hepatic, pulmonary or renal disease
*prior use of Montelukast-within one week of procedure
* Older than 8, younger than 3
*active respiratory infection that causes cancellation of surgery
*ASA III or IV, indicating high risk anesthesia status

Number: Approximately 120 patients will be recruited for the study, 60 from ages 3-5, and 60 from ages 6-8.

PROCESS OF OBTAINING CONSENT

Consent will be obtained at the same time surgical consent is obtained during the outpatient preoperative Otolaryngology clinic visit by study personnel (investigator or designee), or they will be given a letter explaining the study and contacted via telephone to be given more information and have questions answered (by study personnel, investigator or designee). Randomization will be performed after informed consent is obtained. If the parent or legal guardian agrees then the consent will be signed prior to the drug being given in the same day surgery (SDS) area. Parental or guardian permission will be obtained for all potential subjects. The parents/guardians will be informed of the study protocol, risks, and benefits by the investigator or designee. If the parent/guardian has had all their questions answered, they will sign an IRB-approved consent document. They will be advised that the consent is voluntary and the investigator or designee will answer any questions that may arise.

Potential subjects and/or parents/guardians of all potential participants will be given telephone numbers and email addresses to contact the study team with any questions, concerns or the desire to withdraw from the study. They will also be provided with the telephone number of the Institutional Review Board. All CCHMC personnel designated as co-investigators above will be authorized to conduct the consent process.

STUDY INTERVENTIONS

Patients will undergo an adenotonsillectomy or tonsillectomy as indicated by their preoperative contact with their otolaryngologist and other physicians. Patients will be randomly assigned to either the control (Group 1) or treatment group (Group 2) at the time the procedure is scheduled. The order of assignment to groups will be determined by random number generator programmed by the project biostatistician or randomization in a similar fashion. Randomization will be further stratified by age group, including 1) 3-5 years of age 2) 6-8 years of age as previously described. The patients in Group 1 will be given a placebo medication (prepared by the CCHMC investigational pharmacy) 0-3 hours prior to surgery in SDS. The patients in Group 2 will be given an age appropriate dose of Montelukast (prepared by the CCHMC investigational pharmacy) 0-3 hours prior to surgery in the SDS (Table 1). Placebo or drug will be given by the anesthesia service in the SDS room. Patients undergoing adenotonsillectomy will have blood collected prior to the procedure through the placement of an intravenous line (IV) for surgery. Approximately 3 mL of whole blood will be collected in the appropriate blood collection tube. The samples will be processed and the serum or plasma will be stored at the Schubert Research Core (SRC) for future inflammatory biomarker pharmacogenetics testing. Specimens will only be identified by Study name, PI and Study ID. After the procedure is complete patients in both groups will be evaluated bedside for pain using the FLACC scale used at our institution. The FLACC pain levels will be recorded in the EPIC dropdown menu as is our current institutional standard. Patients will then be given a second dose of Montelukast or placebo 9-13 hours post-operatively. Once a study procedure is done, the approved personnel responsible for entering the data into the study database, and for ensuring confidential storage of the data, will be notified and obtain the data directly from EPIC charting. Data will include demographic information including age, sex, race, weight at the time of surgery, comorbidities, and indications for adenotonsillectomy. Intraoperative details such as estimated blood loss, anesthesia, operative time as well as the method and materials used to perform adenotonsillectomy will be obtained. Post-operative

data will be gathered, including adherence to planned protocol, pain scores and complications including post tonsillectomy hemorrhage, fever, otalgia, trismus, nausea/vomiting and death. In addition, rates of postoperative contacts (Emergency department visits or phone calls) for pain related concerns will be evaluated via a scheduled phone call to patient's parents or guardians 3 weeks after surgery.

Age	Age adjusted dose of Montelukast
2-5 y/o	4 mL of 1 mg/mL solution
6-8 y/o	5 mL of 1 mg/mL solution

Table 1: Amount of Montelukast given by age

DATA ANALYSIS/METHODS

Data will be extracted from the electronic medical record, patient paper charts, bedside pain assessments and postoperative phone call. A chi-square analysis will be performed after the first 10 patients are enrolled to insure that complications in Group 2 (treatment group) do not rise above the rates in Group 1 control group). Data will be housed in a password protected database (REDCap), accessible only by approved study personnel.

The primary outcome variable will be the amount of opioid pain medications necessary postoperatively. Secondary outcome variables include postoperative pain scores using the FLACC scale, and the number of patient contacts with an otolaryngology health provider or emergency department provider (Emergency department visits or calls to the otolaryngology nursing hotline) due to pain.

Descriptive statistics will be computed for all demographic data to describe the sample and check for missing and outlying data. Descriptive statistics will also be computed for all measures of study variables. Transformations of non-normally distributed variables will be considered for analyses as indicated. The statistical plan will follow an intent-to-treat analysis. Differences in basic characteristics between the intervention and control groups will be assessed using chi-square (for categorical measures) and t tests (for continuous measures). Nonparametric methods will be considered if deemed appropriate. Data on the number of opioid doses required will be compared between the control and intervention groups using chi-square analysis. Logistic regression will be performed to assess potential confounding, if descriptive statistics indicate confounding may be present. Specific attention will be placed on race of the patient and the number of intraoperative morphine equivalents given. All results will be reported as described by the CONSORT guidelines. All analyses will be performed using SAS software (SAS Institute Inc., Cary NC) at an overall alpha = 0.05 significance level.

Although we expect it to be rare, patients who wish to withdraw from the study will be counted in their initial group for means of intention to treat analysis.

Sample size/Power calculations

Goal is for ratio of control vs. treatment group 1:1 (equal number in both placebo and treatment group). We will plan on using two sided tests to evaluate for differences between treatment groups. To find an N to give adequate power, two pieces of information are needed: The proportion of opioid usage in the placebo group, and the estimated proportion of opioid usage in the treatment group.

P1=true proportion of opioid usage in control, estimated to be 0.6 based on an evaluation of our retrospective data at CCHMC.
P2=true proportion of opioid usage in Montelukast group, estimated to be 0.3 based on previous trials.
Thus, P2-P1=0.6-0.3= 0.3.
The smaller proportion of success (P1) =0.3.

Using standard power determination tables (Gehan, EA, Clinical Trials In Cancer Research, Environ Health Perspect. 1979 Oct; 32: 31–48.): N=44 for power of 0.8 (alpha=0.05), 56 for power of 0.9 (alpha=0.05), and 95 for power of 0.95 (with alpha=0.01) this is an N for each group within the study. For a power of 0.9, 56 patients are needed in each group, or 112 total patients. Given a potential for patients being lost to follow up, our goal recruitment will be 120 patients. This will give a power of 0.9, and looking at significance for alpha=0.05. The appropriate power is designed to detect a 50% reduction in opioid doses given in patients receiving montelukast.

FACILITIES and PERFORMANCE SITES:
Cincinnati Children's Hospital Medical Center (CCHMC), Division of Pediatric Otolaryngology, Head and Neck Surgery, Cincinnati Children's Hospital Medical Center (CCHMC), Division of Molecular genetics.

POTENTIAL BENEFITS
For patients randomized to Group 2 (Montelukast) there is the potential benefit of decreased pain in the postoperative period. For patients randomized to Group 1, there is the potential benefit of the placebo effect.

POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS
There are no potential intervention risks to patients who are randomized to Group 1 (control group) as their care will be conducted in the exact manner as is our current institutional protocol. The main risk of tonsillectomy and adenotonsillectomy is that patients in either group have a risk of post tonsillectomy hemorrhage. While there is no current evidence to suggest that Montelukast increases post tonsillectomy hemorrhage rates, statistical analysis will be performed by chi-square analysis continually after the first 10 patients are enrolled to ensure that complications in Group 2 (Montelukast group) do not rise above the rates in Group 1 (control group). These rates will be reported to the DSMB after the first 10 and then every 6 months. Should rates in the Montelukast group rise above the control group the study will stop until a root-cause analysis of each complication in Group 2 is performed defining the potential role Montelukast played. The potential intervention risks for patients randomized to Group 2 include the known side effects of Montelukast in pediatric populations. Previous data suggests that the following events occur with a frequency more than 2% in patients taking Montelukast, and more

frequently than in pediatric patients who received placebo: fever, cough, abdominal pain, diarrhea, headache, rhinorrhea, sinusitis, otitis, influenza, rash, ear pain, gastroenteritis, eczema, urticaria, varicella, pneumonia, dermatitis, and conjunctivitis.

The most common risk of blood draw is pain or bruising around the IV site, and poses minimal risk to the study participant.

Other reported side effects that may not be caused by the study medicine but have been observed in children taking the study medicine include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor. It is uncertain if these side effects are due to Montelukast, and these side effects have only been seen in patients taking Montelukast on a regular basis.

All of these risks will be discussed during the consent process. Montelukast has been established to be safe in patient populations over 2 years of age by the FDA.

SECURITY

All data including any Protected Health Information (PHI) collected including standard demographic data such as age, sex, race/ethnicity will be stored on the secure REDCap server. Only study personnel authorized by the Primary Investigator will have access to the data. Investigators and research staff will be instructed not to discuss study subjects except as necessary to carry out data collection. At no time will published materials reveal the identities of any patient participating in the study. Reporting of outcomes will be carried out so that patient identification cannot be ascertained.

RISK/BENEFIT ANALYSIS

The risk/benefit ratio is favorable in that risks to the involved patients will be continually monitored and the findings may prove to change practice patterns resulting in improved outcomes. Improving pain control in the postoperative setting will minimize patient discomfort and decrease the amount of opioid pain medication necessary postoperatively. The risk of Montelukast is relatively low given published side-effect data. The risk of blood draws are minimal.

VULNERABLE POPULATIONS

The rights and welfare of children involved in this research study will be protected as outlined in 45 CFR 46, Subpart D.
Employees of CCHMC will be free to give consent for their child/legal minor to participate in this research study, but no incentives or disincentives will be offered.

DATA SAFETY & MONITORING

A Data Safety and Monitoring Board (DSMB) will be composed of two attending physicians familiar with the procedure who are not directly involved with the study and post-operative management (1 Otolaryngology faculty and 1 Anesthesia faculty), as well as a biostatistician. Adverse events will be classified as serious include: severe allergic reaction, severe bleeding, suicidal ideation, or a death within the study period. Adverse

events will be collected by study personnel until the 3-4 week follow up phone call routinely performed by the Otolaryngology department. Each serious safety event will be reported to the DSMB within 5 days for monitoring. If a serious safety event occurs, a root cause analysis has to be performed, the study will be interrupted, and there will be no subjects enrolled at this time. Enrollment will resume after it has been assessed and approved by the DSMB.

Statistical analysis will be performed by chi-square analysis continually after the first 10 patients are enrolled to insure that complications in Group 2 (Montelukast group) do not rise above the rates in Group 1 (control group). This will be sent to the DSMB for review. These rates will be reported to the DSMB every 6 months. Should rates of complications in the Montelukast group rise above the control group the study will stop until a root-cause analysis of each complication in Group 2 is performed defining the potential role Montelukast played.

The study will be suspended or closed if any of the following occurs: Accrual has been met, the study objectives have been met, the PI believes it is not safe to continue the study, the DSMB chair recommends enrollment be suspended pending further review from the DSMB, the DSMB recommends the trial be closed, or the NIH, FDA or CCHMC IRB suspends or closes the trial. If either death or another serious adverse event occurs, enrollment will be suspended and the DSMB chair will review the data within 5 calendar days. Following review, the DSMB chair can approve re-starting enrollment, or they can defer to the full DSMB for approval. In the event that the DSMB Chair approves the re-start of enrollment, this information will be detailed in the next regularly scheduled DSMB meeting. In the event that the DSMB Chair defers approval, the DSMB will review the data within 14 calendar days. The DSMB will be sent data every 6 months for review and will meet once a year to discuss data unless an adverse event warrants additional meetings.

PRIVACY and CONFIDENTIALITY

Data collection will necessarily include individually identifiable information into a REDCAP database. Data will be extracted and incorporated into a secure, password-protected spreadsheet file, computer files will be password-protected and only study personnel will have access to the database. Investigators and research staff will be instructed not to discuss study subjects except as necessary to carry out data collection. At no time will published materials reveal the identities of any patient participating in the study.

FUTURE USE

The database will be maintained indefinitely and may be used for future unknown research

COMPENSATION/REIMBURSEMENT FOR PARTICIPATION

There is no compensation or reimbursement for participation in the study. The study participants will not be additionally inconvenienced or have additional visits to CCHMC for purposes of the study. Study drug (montelukast or placebo) will be paid for by the research study. The blood draw via IV will not be billed to the patient and/or their insurance. Participants and/or their insurance companies will be billed for all clinical costs related to having the adenotonsillectomy procedure.

COSTS ASSOCIATED WITH PARTICIPATION

There are no monetary costs associated with participation in the study for patients. No diagnostic tests or procedures will be performed solely for the purpose of the study.

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