Children's Hospital of Philadelphia

Informed Consent and HIPAA Authorization Form

Study Title: Opioid-free versus traditional anesthetic with opioids for tonsillectomy

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You, or your child, may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of this research study, and the risks and possible benefits of participating.

In the sections that follow, the word "we" means the study doctor and other research staff. If you are a parent or legal guardian who is giving permission for a child, please note that the word "you" refers to your child.

Study Overview

You are being asked to take part in this research study because you are scheduled for a tonsillectomy. Your surgeon has already talked to you about the risks of tonsillectomy that include bleeding, poor pain control, dehydration and readmission.

The purpose of this study is to find out if non-opioid medications (Ketorolac and Dexmedetomidine) could provide the same amount of pain control as compared to standard of care opioid medication during tonsillectomy. Neither of these medications are FDA approved for tonsillectomy or approved for use in children. However, these medications are used in CHOP's clinical pediatric anesthesia practice.

If you agree to take part, your participation will last for up to thirty days after your surgery. As a participant in the research you will:

- Be randomly assigned to one of two investigational groups, and you will not know to which you've been assigned:
  - Group 1: (Traditional care group – TCG) Receive regular pain care with opioid medications by IV during surgery, and other therapies including non-steroidal anti-inflammatory medications or acetaminophen by mouth in the hospital and at home or
  - Group 2 - Opioid-free group (OFG) Receive IV non-steroidal anti-inflammatory medication – Ketorolac and Dexmedetomidine during surgery and other therapies including non-steroidal anti-inflammatory medications or acetaminophen by mouth in the hospital and at home
- Complete questionnaires

Standard pain treatment for tonsillectomy often includes opioids. These are given with or without oral non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and/or

acetaminophen. We are asking you to participate in a study of a single dose of intravenous NSAID called Ketorolac. This will replace the dose of opioid after surgery.

After this single dose, you will receive the usual treatment given to patients after tonsillectomy. In some studies, there has been a higher risk of bleeding with Ketorolac. This was seen especially in adults when given multiple doses and at higher doses than we will use in this study. Ketorolac is not approved by the FDA for use in children. Studies in children have shown some increased risk of bleeding but not after a single dose. There is also the risk of kidney damage when you take any NSAID. This can happen if you are not drinking and not making enough urine. If you choose not to participate in this study, your surgeon will give you a different NSAID (not Ketorolac) that is swallowed by mouth. This could be Ibuprofen (Advil, Motrin) or Celecoxib (Celebrex) and acetaminophen (Tylenol). You could also get an opioid medication like morphine, or oxycodone. If your pain is not well controlled after your initial treatments, you may also be given opioid pain medications. This would happen no matter which group you are in to treat your pain better.

Dexmedetomidine is part of a group of medications that provide pain control and can make you sleepy. The main risk is a decrease in heart rate; other risks include low or high blood pressure and a high heart rate. It is not FDA-approved for this indication.

If you are assigned the opioid-free group, you might benefit if the use of ketorolac results in taking less opioids (and therefore experiencing fewer opioid related side effects such as nausea, vomiting and itching, etc). If you are assigned to the traditional care group, you might benefit if standard care results in better pain relief and will avoid the possible side effects (e.g. bleeding, kidney issues, etc) that could result from administration of ketorolac. This research will help us better understand how to use opioid free medicines for tonsillectomies in children.

If there is anything in this form you do not understand, please ask questions. Please take your time. You do not have to take part in this study if you do not want to. If you take part, you can leave the study at any time. If you do not choose to take part in this study, you can discuss treatment options with your doctor. Please see below for additional details about the study.

How many people will take part?

About 550 children will take part in this study at CHOP.

What is the current standard of treatment for this disease?

Currently, all children undergoing tonsillectomy receive at least one opioid medication (such as Morphine and Fentanyl), along with a possible combination of one to three of the following medications: Acetaminophen, Dexmedetomidine, and a non-steroidal anti-inflammatory different from Ketorolac. Medication selection currently depends on your doctor's preference.

What are the study procedures?

Randomization: You will be randomly assigned to either the Traditional care group with opioids or the opioid-free group starting with Dexmedetomidine and then Ketorolac. This means that the physician or anesthesiologist will not get to decide which group you will

be assigned to. There is an equal chance of being in either group, just like flipping a coin. You will not know to which group you are assigned. Your initial therapy will be different depending on the group you are in but you will receive additional therapies, including acetaminophen (Tylenol), non-steroidal anti-inflammatories (ibuprofen – Advil) and possibly an opioid (oxycodone, morphine) to control your pain if needed.

Study medication administration: The study groups differ based upon the medications that you will receive in the operating room.

- Group 1: The Traditional care group (TCG) receives morphine or fentanyl through the IV that is placed for surgery
- Group 2: The opioid free group (OFG) receives Ketorolac and Dexmedetomidine (neither of which are FDA-approved but are commonly used at CHOP for other surgeries) through the IV.

All patients will receive intravenous Acetaminophen (Tylenol). You may also receive medication by mouth in the recovery room, if needed.

Study Monitoring and Assessment: You will be monitored and assessed at 15 and 30 minutes after waking up from surgery to ask you about your pain control and any side-effects. You will receive standard of care pain medications after surgery, which could include intravenous opioids if your pain is considered to be severe.

Questionnaires: You will be asked to answer a questionnaire before surgery on the day of surgery, and post-operative days 1 and 5 after surgery to ask how you are feeling and what other medications you have used. You will also receive a phone call from the hospital the morning after surgery to make sure that you are doing well, and it is important to pick up the phone so that we can check on you. You will also receive a brief questionnaire on Day 30 to make sure you did not need medical care outside of CHOP. The questionnaire can be completed on a paper form or over the phone and will take about 15 minutes, or text or email with a link to the online questionnaire which takes less than 5 minutes.

Medical records review: We will review your medical records throughout the study to collect baseline medical information, detailed anesthesia information, surgical records, surgical recovery, and post-operative follow up information up to 30 days after surgery.

Procedures that are not changed by this study: Your surgery, your postoperative pain management, and all other postoperative care, are standard care and will not be changed by your being in this study. You will receive oral medications and possibly intravenous opioid medications in the recovery room if your pain is severe. Your surgeon will prescribe oral pain medications for use at home in the usual manner.

What will be done with my data during this study?

During the study, we will collect information from you (data). By agreeing to participate in this study, you agree to give this information to CHOP for research purposes.

What are the risks of this study?

Taking part in a research study involves inconveniences and risks. The main risks of taking part in this study are discussed below.

Risks Associated with Randomization: It is not known which treatment works best in managing pain. The treatment group you are assigned to may prove less effective or have more side effects than the other study group.

Risks of Both Groups: Hemorrhage is not rare after tonsillectomy. At CHOP, 2-5% of all tonsillectomies develop bleeding after surgery with usual care. You will be monitored during the study for such events. Additionally, your hospital stay might last longer due to your participation in the study and/or you might need to be re-admitted. Up to 10% of patients are readmitted with side effects from narcotics (vomiting), pain-related complications (uncontrolled pain, dehydration) or bleeding. Both groups may receive opioid pain medications after surgery if they are needed to control your pain.

Traditional Care Group - Risk of Opioid administration: Opioid medications are now given to all children at CHOP during their tonsillectomy surgery. Risks include nausea, vomiting, itching, constipation, decreases in oxygen levels and slow breathing. If you develop the last two, you might receive oxygen or a medication called Naloxone (Narcan) to treat these symptoms.

OF Group - Risks of Ketorolac: While Ketorolac is given to children at CHOP in other departments, such as Urology and Orthopedic Surgery, and is given at some other children's hospitals for tonsillectomy, it is not FDA approved for use in children. It is not routinely given for tonsillectomy at CHOP due to concerns about bleeding based on previous studies done mostly in adults. There is some risk of bleeding after tonsillectomy with all non-steroidal anti-inflammatory drugs (NSAIDs), and it may be somewhat higher with the only available IV formulation Ketorolac. A large review suggests that Ketorolac use is not associated with an increased risk of bleeding in children under age 18 but did find a higher risk of bleeding in adults. Ketorolac is well known to provide substantial relief of pain after surgery and this study is being conducted to find out if the pain relief from ketorolac is good enough and can be used safely to reduce pain and the need for opioid medications after surgery.

After surgery all study participants will be given acetaminophen, possibly more NSAIDs by mouth (Ibuprofen –(Advil) or Celecoxib (Celebrex), and possibly an opioid medication like Oxycodone or Morphine if needed to control pain. Uncommon side effects related to all NSAIDs including Ketorolac, Naproxen (Aleve), and Ibuprofen (Advil) include: headache, stomach pain, lightheadedness, fatigue and diarrhea. Although extremely rare, Ketorolac has a boxed warning for peptic ulcers, increased risk of bleeding, stomach bleeding, and holes in the stomach. The rare risks of taking NSAIDs include life-threatening, potentially fatal skin adverse events and hypersensitivity, including breathing distress caused by narrowing of the airways and anaphylaxis, which is a serious, potentially life-threating allergic reaction that can occur in any patient. Patients with known sensitivity to NSAIDS cannot join the study. There is an extremely rare risk of heart attack and stroke seen in adults taking NSAIDs; this is not expected in healthy children and is higher risk with patients who have known heart disease or risk factors or those who receive high doses. All NSAIDs, like Ketorolac, naproxen and ibuprofen, have these same risks. There is a specific boxed warning of the risk of increased bleeding in patients that have medical problems that are linked to higher bleeding risk, which is why these patients are also excluded from participating in the study. To be clear, if you are assigned to the OFG group, you will only receive one dose of Ketorolac during surgery.

OF Group - Risks of Dexmedetomidine: Dexmedetomidine is part of a group of medications called Alpha-2 agonists. It provides pain control and can make you sleepy. The label states that rarely patients can have a lower breathing rate; however, at CHOP, Dexmedetomidine is often used for sedation and pain control because the risk of lower breathing rates is less than what is seen with opioids . The main risk is a decrease in heart rate; other risks include low or high blood pressure and a high heart rate. If you have heart disease or certain genetic syndromes that have higher risk of low heart rate, you will not be eligible to participate. Your heart rate will be closely monitored during and after surgery. In the very rare event you developed a low heart rate, you would receive medication to treat it.

OF Group - Risk of the combination of Ketorolac and Dexmedetomidine: There is no known increased risk of giving these two medications together.

Risk of Acetaminophen: Acetaminophen, or Tylenol, is a medication commonly given to children. In children with liver problems, it can make them worse. You will not receive Acetaminophen if you have certain liver problems.

Risks of Medical Record Review, Questionnaires, and Monitoring and Assessment: As with any study involving collection of data, there is the possibility of breach of confidentiality of data. Every precaution will be taken to secure participants' personal information to ensure confidentiality.

At the time of participation, each participant will be assigned a study identification number. This number will be used on data collection forms and in the database instead of names and other private information so they cannot be identified without a key. A separate list will be maintained that will link each participant's name to the study identification number .

Are there any benefits to taking part in this study?

If you are assigned to OF group and do not need opioids after your surgery to control your pain, you may benefit directly with taking less opioids and fewer opioid related side effects such as nausea, vomiting and itching. If you are assigned to the traditional care group, you may benefit if standard care results in better pain relief and will be spared the possible side effects (e.g. bleeding, kidney issues, etc) that could result from administration of ketorolac. However, we cannot guarantee or promise that you will receive any direct benefit by participating in this study. The knowledge gained from this study may help doctors determine if an opioid-free anesthetic provides equal pain relief to a standard opioid-containing anesthetic for pain management associated with tonsillectomy.

Do you need to give your consent in order to participate?

If you decide to participate in this study, you must sign this form. A copy will be given to you to keep as a record.

What are your responsibilities?

Please consider the study time commitments and responsibilities as a research subject when making your decision about participating in this study.

What happens if you decide not to take part in this study?

Participation in this study is voluntary. You do not have to take part in order to receive care at CHOP.

If you decide not to take part or if you change your mind later there will be no penalties or loss of any benefits to which you are otherwise entitled.

Can you stop your participation in the study early?

You can stop being in the study at any time. You do not have to give a reason.

What choices do you have other than this study?

There are options for you other than this study including standard management for tonsillectomy.

What about privacy, authorization for use of Personal Health Information (PHI) and confidentiality?

As part of this research, health information about you will be collected. This will include information from medical records and the surveys. Information related to your medical care at CHOP will go in your medical record. Medical records are available to CHOP staff. Staff will view your records only when required as part of their job. Staff are required to keep your information private. Information that could identify you will not be shared with anyone - unless you provide your written consent, or it is required or allowed by law. We will do our best to keep your personal information private and confidential. However, we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The results of this study may be shown at meetings and published in journals to inform other doctors and health professionals. We will keep your identity private in any publication or presentation.

Several people and organizations may review or receive your identifiable information. They will need this information to conduct the research, to assure the quality of the data, or to analyze the data or samples. These groups include:

- Members of the research team and other authorized staff at CHOP;
- People from agencies and organizations that perform independent accreditation and/or oversight of research; such as the Department of Health and Human Services, Office for Human Research Protections;
- The Food and Drug Administration.

By law, CHOP is required to protect your health information. The research staff will only allow access to your health information to the groups listed above. By signing this document, you are authorizing CHOP to use and/or release your health information for this research. Some of the organizations listed above may not be required to protect your information under Federal privacy laws. If permitted by law, they may be allowed to share it with others without your permission.

There is no set time for destroying the information that will be collected for this study. Your permission to use and share the information and data from this study will continue

until the research study ends and will not expire. Researchers continue to analyze data for many years and it is not possible to know when they will be completely done.

Can you change your mind about the use of personal information?

You may change your mind and withdraw your permission to use and disclose your child's health information at any time. To take back your permission, it is preferred that you inform the investigator in writing.

Dr. Tori Sutherland
The Children's Hospital of Philadelphia
Department of Anesthesiology and Critical Care
34th Street and Civic Center Blvd.
Philadelphia, PA 19104

In the letter, state that you changed your mind and do not want any more of your health information collected. The personal information that has been collected already will be used if necessary for the research. No new information will be collected. If you withdraw your permission to use your personal health information, you will be withdrawn from the study.

Financial Information

Will there be any additional costs?

The costs associated with drugs administered for your participation in this study will be billed to you or your insurance. Additionally, while you are in this study, the cost of your usual medical care – procedures, medications and doctor visits – will continue to be billed to you or your insurance. It is possible that you may receive one more or one less medication that you would normally receive, but we do not expect a difference in your bill. We can help you understand your financial responsibilities.

- If your insurance does not pay for all the costs, you may be responsible for the remaining costs, including any co-payments and deductibles as required by your insurance.
- If you do not have insurance, you will be responsible for the costs of taking part of this study.

CHOP has programs to help uninsured and underinsured families see if financial assistance is available. If you need financial assistance, you can talk with a financial coordinator.

Will you be paid for taking part in this study?

You will not receive any payments for taking part in this study.

Who is funding this research study?

The Division of Anesthesiology and Critical Care at The Children's Hospital of Philadelphia is partially funding this research along with a Foerderer Fund of Excellence grant and a McCabe Grant.

Please ask Dr. Tori Sutherland if you have any questions about how this study is funded.

What if you have questions about the study?

If you have questions about this study or how your data are going to be used, call the study doctor, Dr. Tori Sutherland at 267-426-2961. If the matter is urgent, you may have the hospital operator page Dr. Sutherland directly if there is no response at the number listed above. You may also talk to your own doctor if you have questions or concerns.

The Institutional Review Board (IRB) at The Children's Hospital of Philadelphia has reviewed and approved this study. The IRB looks at research studies like these and makes sure research subjects' rights and welfare are protected. If you have questions about your rights or if you have a complaint, you can call the IRB Office at 215-590-2830.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What happens if you are injured during the study?

If you are hurt or get sick from something that was done as part of this study, doctors at the clinic or hospital can arrange for emergency medical care. The Hospital does not offer financial compensation or payment for injuries due to participation in this research.

You and your insurance company will be billed for the costs of any care or injuries.

If you think you have been injured from taking part in this study, call Dr. Sutherland at 267-426-2961. She can go over things with you, let you know of resources that may be available and give you information on what you need to do.

In case of injury resulting from this study, you will not lose any legal rights by signing this form.

What will be done with my data when this study is over?

We will use and may share data for future research. They may be shared with researchers/institutions outside of CHOP. This could include for profit companies. We will not ask for your consent before using or sharing them. We will remove identifiers from your data, which means that nobody who works with them for future research will know who you are. Therefore, you will not receive any results or financial benefit from future research done on your specimens or data.

Consent to Take Part in this Research Study and Authorization to Use and Disclose Health Information for the Research

The research study and consent form have been explained to you by:

Person Obtaining Consent	Signature of Person Obtaining Consent
	Date

By signing this form, you are indicating that you have had your questions answered, you agree to take part in this research study and you are legally authorized to consent to your child's participation. You are also authorizing the use of your/your child's health information as discussed above. If you don't agree to the collection, use and sharing of health information, you cannot participate in this study. **NOTE:** *A foster parent is not legally authorized to consent for a foster child's participation.*

Name of Subject	
Signature of Subject (18 years or older)	Date
Name of Authorized Representative (if different than subject)	Relation to subject: ☐ Parent ☐ Legal Guardian
Signature of Authorized Representative	Date

Child Assent to Take Part in this Research Study

For children capable of providing assent:

I have explained this study and the procedures involved to _____ in terms he/she could understand and that he/she freely assented to take part in this study.

_____
Person Obtaining Assent

_____ _____
Signature of Person Obtaining Assent Date

This study has been explained to me and I agree to take part.

_____ _____
Signature of Subject (optional) Date

For children unable to assent:

I certify that _____ was not capable of understanding the procedures involved in the study sufficiently to assent to study participation.

_____
Person Responsible for Obtaining Assent

_____ _____
Signature of Person Responsible Date