NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

STUDY TITLE: Prospective Hemodynamic and Pharmacokinetic Analysis of Oxymetazoline Absorption during Functional Endoscopic or Turbinate Reduction Surgery or Adenoidectomy.

PRINCIPAL INVESTIGATOR: Richard Cartabuke, MD

CONTACT TELEPHONE NUMBER: 614-722-4200 (Monday – Friday, 8 am – 4:30 pm)

SUBJECT'S NAME: _____ DATE OF BIRTH: _____

NOTE: The words "you" and "your" are used in this consent form. These words refer to the study volunteer whether a child or an adult.

1) INTRODUCTION

We invite you to be in this research study because you are having nasal surgery or having your adenoids removed.

Participation is voluntary. Using this form as a guide, we will explain the study to you. If you have any questions about the study, please ask. Once you understand this study, we will ask you to decide whether you would like to participate or not. By signing this form, you agree to be in this study. If you do not want to be involved with this study, all regular and standard medical care will still be available to you here or at another institution. You also have the right to leave this study at any time, even if you agree to join now.

If this study involves a child between 9 and 18 years of age, the child will receive an explanation of the study in a separate form, called an Assent form. If they agree to be in the study, they will be asked to sign this form.

You will be given a signed and dated copy of the consent and the assent form.

2) WHY ARE WE DOING THIS RESEARCH STUDY?

Oxymetazoline (Afrin®) is a nasal spray to relieve stuffiness in the nose. During nasal or sinus surgery, Afrin is squirted on small cotton pads that are then packed into the nose to decrease swelling and stop bleeding. During adenoid removal, Afrin is squirted in the back of the throat to decrease swelling and stop bleeding.

This is a study to find out how much of the medicine is absorbed by the body through the nasal passages or throat and how long it lasts in the body. We also want to see if it has any other effects on the body.

3) WHERE WILL THE STUDY BE DONE AND HOW MANY SUBJECTS WILL TAKE PART?

This study will be done at Nationwide Children's Hospital and we hope to enroll 30 participants.

4) WHAT WILL HAPPEN DURING THE STUDY AND HOW LONG WILL IT LAST?

This study will consist of one visit and will last during the time of your surgery and recovery, or between 2½ and 4 hours. You will be taken to surgery and be put to sleep. You will have an intravenous catheter (IV) placed in your arm. At the end of the surgery the surgeon will pack your nose with small cotton pads that have been soaked with Afrin or squirt Afrin in the back of your throat. **This is all standard of care.**

As part of the study, you will have a second IV started in your other arm so that we can collect blood without sticking you multiple times. This will occur after you are asleep. We will collect 3 mL (⅔ teaspoon) of blood from this IV at 6 different times during the study. This is to measure the amount of Afrin in your body. One or more of these blood draws may be after you are awake in the recovery room or post-op area. The total amount of blood drawn will be approximately 1¼ tablespoons.

We will be recording your heart rate and blood pressure. We will also record any other medications that you are given during surgery and in the recovery room.

5) WHAT ARE THE RISKS OF BEING IN THIS STUDY?

Drawing blood and starting IVs by placing a needle in a vein may cause pain, lightheadedness, fainting, bleeding, bruising, or swelling at the puncture site. Infection is a rare possibility.

There may be other risks of being in this research study that are not known at this time.

6) ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

Although there will be no benefit to you from being in this study, we hope to learn something that could help others.

7) WHAT ARE THE COSTS AND REIMBURSEMENTS?

All costs related to the research parts of this study (blood draws and processing blood samples) will be covered by the research team. However, the parts of the study that would be done for routine clinical care (surgery and medications) will be billed to you and to your insurance company or third party payer. You may have to pay any costs that the insurance company or third party payer does not pay. The study team will discuss these costs with you.

8) WHAT HAPPENS IF BEING IN THIS STUDY CAUSES INJURIES?

If your child is hurt by the procedures that are part of the Study, you should seek medical treatment for the injuries and tell the Principal Investigator as soon as possible at the number on the first page of this form. If it is an emergency, call 911 or go to the nearest emergency department.

In most cases, this care will be billed to your health insurance company or whoever usually pays for your health care at the usual charges, but some insurance companies will not pay for care related to a study. If the care is provided at Nationwide Children's Hospital, we make no commitment to pay for the medical care provided to you. No funds have been set aside to compensate you in the event of injury. If no one else pays for your care, you may have to pay for the cost of this care. This does not mean that you give up any of your legal rights to seek compensation for your injuries.

9) WHAT HAPPENS IF I DO NOT FINISH THIS STUDY?

It is your choice to be in this study. You may decide to stop being in this study at any time. If you stop being in the study, there will not be a penalty or loss of benefits to which you are otherwise entitled.

10) OTHER IMPORTANT INFORMATION

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

The final study results will not be shared with you individually. However, at some time, a final study summary will be available on the ClinicalTrials.Gov (http://clinicaltrials.gov) website.

Nationwide Children's Hospital is a teaching hospital and we are committed to doing research. Doing research will enable us to learn and provide the best care for our patients and families. You may be asked to participate in other research studies in the future. You have the right to decide to participate or decline to participate in any future studies. We will not share your contact information with researchers outside Nationwide Children's Hospital.

11) HOW WILL MY STUDY INFORMATION BE KEPT PRIVATE?

Information collected for this study may include information that can identify you. This is called "protected health information" or PHI. By agreeing to be in this study, you are giving permission to Dr. Richard Cartabuke and the study staff to collect, use, and disclose your PHI for this research study and for future research purposes (including purposes that are currently unknown) unless otherwise allowed by applicable laws. Information collected is the property of Nationwide Children's Hospital or one of its affiliated entities or the Sponsor.

The reason why this PHI is collected, and what information will be used is listed below. The PHI will only be shared with the groups listed, but if you have a bad outcome or adverse event from being in this study, the Principal Investigator and staff or other health care providers may need to look at your entire medical records. In the event of any publication regarding this or any future studies, your identity will not be revealed.

The PHI collected or created under this research study will be used or disclosed as needed until the end of the study. The records of this study will be kept for an indefinite period of time and your authorization to use or disclose your PHI will not expire.

PHI that may be used or disclosed: Name; Birth Date; Date Surgery; Medical Record Number.

People or Companies authorized to use, disclose, and receive PHI collected or created by this research study:

- PI and study staff
- The Nationwide Children's Hospital Institutional Review Board (the committee that reviews all human subject research)
- Nationwide Children's Hospital internal auditors

Because of the need to give information to these people, absolute confidentiality cannot be guaranteed. Information given to these people may be further disclosed by them and no longer be protected by federal privacy rules.

Reason(s) why the use or disclosure is being made: to locate medical charts and to be able to analyze the data.

You may decide not to authorize the use and disclosure of your PHI. However, if it is needed for this study, you will not be able to be in this study. If you agree to be in this study and later decide to withdraw your participation, you may withdraw your authorization to use your PHI. This request must be made in writing to the Principal Investigator at:

Richard Cartabuke, MD
Nationwide Children's Hospital
Department of Anesthesiology & Pain Medicine
700 Children's Drive, J2374
Columbus, OH 43205

If you withdraw your authorization, no new PHI may be collected and the PHI already collected may not be used unless it has already been used or is needed to complete the study analysis and reports.

12) WHOM SHOULD I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have questions about anything while on this study or you have been injured by the research, you may contact the Principal Investigator at Dr. Richard Cartabuke at (614) 722-4200, Monday – Friday, between 8 am – 4:30 pm.

If you have questions, concerns, or complaints about the research; if you have questions about your rights as a research volunteer; if you cannot reach the Principal Investigator; or if you want to call someone else - please call (614) 722-2708, Nationwide Children's Hospital Institutional Review Board, (IRB, the committee that reviews all research involving human subjects at Nationwide Children's Hospital).

Subject's Name _____Date of Birth_____

SUBJECT or SUBJECT'S PARENT OR PERSON AUTHORIZED TO CONSENT ON BEHALF OF THE CHILD (SUBJECT TO THE SUBJECT'S GENERAL MEDICAL CARE)

I have read this consent form and I have had an opportunity to ask questions about this research study. These questions have been answered to my satisfaction. If I have more questions about participating in this study or a research-related injury, I may contact the Principal Investigator. By signing this consent form, I certify that all health information I have given is true and correct to the best of my knowledge.

I have been given a copy of the Nationwide Children's Hospital Notice of Privacy Practices. If allowed by law, I understand that my right to any information that is created or collected by Nationwide Children's Hospital for this study can be temporarily suspended if necessary for the purposes of this research project. I also understand that my right to access to this information from this study will be reinstated upon completion of this research unless I have been told by the Principal Investigator that I will not receive study results.

I agree to participate in this study or I give permission for my child to participate in this study. I will be given a copy of this consent form with all the signatures for my own records.

CONSENT SIGNATURES

_____ _____
SUBJECT or SUBJECT'S LEGAL REPRESENTATIVE **DATE & TIME AM/PM**

_____ _____
SUBJECT or SUBJECT'S LEGAL REPRESENTATIVE **DATE & TIME AM/PM**

Permission of the second parent not obtained because (select all that apply):
_____ Not required by the IRB (risk level 1 or 2).
_____ Other parent is deceased.
_____ Other parent is unknown.
_____ Other parent is not reasonably available.
_____ Only one parent has legal responsibility for the care and custody of subject.

_____ _____
PERSON OBTAINING CONSENT **DATE & TIME AM/PM**

I certify that I have explained the research, its purposes, and the procedures to the subject or the subject's legal representatives before requesting their signatures.

INVESTIGATORS: Richard S. Cartabuke MD, MBA; Joseph Tobias MD; Charles Elmraghy MD; Julie Rice, BSN, RN, CCRC

Title: Prospective Hemodynamic and Pharmacokinetic Analysis of Oxymetazoline Absorption during Functional Endoscopic or Turbinate Reduction Surgery or Adenoidectomy.

Background and Significance:

Oxymetazoline is an α-adrenergic agonist that is commonly used as a topical sympathomimetic agent in over-the-counter decongestant sprays. Its vasoconstrictive action on the blood vessels defines its clinical utility as both a decongestant and a topical hemostatic agent(1). It is used extensively by otolaryngologists for functional endoscopic sinus surgery (FESS), turbinate surgery, and adenoidectomy to produce vasoconstriction. Riegle et al. compared cocaine 4%, phenylephrine 0.25%, and oxymetazoline 0.05% for nasal vasoconstriction in pediatric patients undergoing functional endoscopic sinus surgery (2), Children who were treated with oxymetazoline had less bleeding and improved visualization compared with the other two vasoconstrictors. Heart rate decreased, but blood pressure was unchanged during the first ten minutes after application. However, the authors did not determine the cumulative dose of oxymetazoline. Although there is generally limited vascular absorption, when administered in larger doses, uptake of oxymetazoline can lead to significant systemic hemodynamic effects, most commonly hypertension related to its action on the α-adrenergic receptors of the smooth muscle of the vasculature that results in vasoconstriction. Furthermore, when used in even larger doses in young children, oxymetazoline can activate central adrenergic receptors and lead to serious adverse effects including cardiovascular instability, respiratory depression, and neurologic complications, which may be potentially life-threatening (3-6) In the operating room, this reflex bradycardia may not always occur because general anesthetics, particularly volatile anesthetics, attenuate the baroreceptor response. Bradycardia may also be a consequence of the direct action of oxymetazoline on central α adrenergic receptors in the locus ceruleus and central vasomotor areas of the brainstem. Our institution recently reported a case of oxymetazoline induced postoperative hypertension in a three year old child following inferior turbinate reduction and adenoidectomy. (7)

Giannakopoulos studied the cardiovascular effects and pharmacokinetics of an intranasal 3 percent tetracaine/0.05 percent oxymetazoline spray at two different dose levels in adult dental patients. (8) A small decrease in heart rate and a small increase in diastolic blood pressure was noted. Serum levels of oxymetazoline were measured and a half-life of 1.72 to 2.32 hours was noted. No similar pharmacokinetic studies have been reported in children. Latham and Jardine reported oxymetazoline-induced hypertension in a 4-year-old child. (9) They also sought to investigate alterations in the amount of medication delivered based on the delivery method. There was up to a 75-fold increase in the volume of medication administered when the bottle was held inverted. Squeezing the bottle in the upright position resulted in a mist with the delivery of 28.9 ± 6.8 μl of fluid. The amount delivered was effort independent. When the bottle was inverted and squeezed, the volume administered was effort dependent.

Current practice at NCH is to soak nasal pledgets with full strength oxymetazoline and insert a varying number of pledgets on the nasal turbinates or into the sinuses for hemostasis, or on the adenoid bed.

This proposed study will assess the hemodynamic effects and measure the systemic absorption of topically applied oxymetazoline in patients undergoing functional endoscopic sinus surgery, turbinate surgery, or adenoidectomy.

Specific Aims/Objectives:
The primary objective is to determine the perioperative hemodynamic effect of oxymetazoline applied topically for vasoconstriction in patients undergoing functional endoscopic sinus surgery, turbinate surgery or adenoidectomy using blood pressure and heart rate intraoperatively (OR) and postoperatively (PACU) until discharge from phase 1 of the PACU.

A secondary objective is to measure the plasma concentrations of oxymetazoline at discrete time periods from instillation and correlate with hemodynamic effects, as well as determine the rate of decline in levels as a function of time.

A secondary objective is to assess the degree of bleeding and ease hemostasis rated by a single observer to minimize variability.

Hypotheses:
Instilled oxymetazoline causes an increase in blood pressure in the intraoperative and postoperative period and, though absorption is rapid and variable, effects are related to serum level of oxymetazoline.

The decline in hemodynamic effect and serum levels is a function of time.

Hemostatic effect is determined by dose of oxymetazoline instilled by the surgeon.

Methods:
Thirty patients of Dr. Charles Elmaraghy who will undergo functional endoscopic sinus surgery, turbinate surgery or adenoidectomy and are anticipated to receive oxymetazoline-soaked pledgets for hemostasis will be enrolled.

Patients ages 2 through 18 yrs. will be enrolled if they are scheduled for

1) Functional endoscopic sinus surgery (ten patients)
2) Turbinate reduction (with or without tonsillectomy and/or adenoidectomy) (ten patients)
3) Adenoidectomy (ten patients)

Patients will be excluded if they have been treated with oral decongestants or antihistamines within 24 hours of surgery, are taking anticoagulants, have a history of nasal trauma within past 3 months, have a history of epistaxis within past 3 months, have a history of hypertension or cardiac disease, or are allergic to oxymetazoline.

There will be no change in the conduct of the general anesthetic care related to the study protocol. Our usual practice will be followed. For premedication, midazolam (0.5 mg/kg to a maximum of 15 mg) will be administered 15-45 minutes prior to the procedure at the discretion of the attending anesthesiologist. An inhalation induction with sevoflurane or an intravenous induction with propofol will be performed by the attending anesthesiologist and titrated to attempt to maintain the bispectral index (BIS) between 40 and 60 to ensure adequate and similar depth of anesthesia. It will not be considered a protocol violation if the BIS is not maintained at this level. Fluid will be administered to

attempt a total of 15 ml/kg for procedures less than 1 hr or maintenance plus replacement for procedures greater than 1 hr. It will not be considered a protocol violation if this amount of fluid is not infused.

Blood pressure and heart rate and will be recorded at 5 min intervals until discharge from PACU or final blood draw, whichever comes first.

Blood samples will be drawn at approximately 5 (3-6 min), 10 (8-12 min), 20 (18-22 min), 45 (30-60 min), 90 (75-120 min) and 150 (135-240 min) minutes via a second IV, placed after the induction of anesthesia. Each sample will be collected in a 3 ml heparin green-top tube. The maximum volume per patient is 18 ml, which is 1.2 tablespoons of blood or approximately 1.5% of the total blood volume in a 2 yr old. This a fraction of the usual blood loss associated with sinus, turbinate, and adenoid surgery. If patient is ready to be discharged from PACU prior to the completion of blood sampling, the sampling will be discontinued and the second IV will be removed.

Plasma Samples

Collection

1. Collect blood sample to analyze oxymetazoline plasma concentrations using a 3 mL - draw green-top Vacutainer® Hemogard collection tube containing heparin.
2. Immediately following collection, gently invert blood sample 8-10 times to mix the anticoagulant in the tube with the blood and place on ice. Separate plasma using standard centrifugation procedures (centrifuge tube approximately 10-15 minutes at 2000g). If plasma has not completely separated, re-centrifuge the specimen for an additional 3-4 minutes. Transfer duplicate plasma aliquots of approximately equal volume. Samples will be stored immediately after plasma separation and may be kept in a dedicated refrigerator at +5 ± 2° C.
3. A minimum of 250 µL plasma will be required.

Processing

1. Transfer duplicate plasma aliquots of approximately equal volume, using standard laboratory technique, into two appropriately-labeled polypropylene tubes (A and B) with screw caps.
2. Labels should be secured to each storage tube using a strip of tape wrapped completely around the tube. Labels should contain the following information: Protocol and study numbers; subject number; study day and time of sample collection; aliquot (Aliquot A or Aliquot B); sample ID (as provided by Sponsor) and biological matrix to be analyzed (whole blood).

Storage

1. Store plasma aliquot A and plasma aliquot B samples in a GLP-compliant freezer at -70°C. Plasma should not be stored at room temperature at all and at +5 ± 2° C for no longer than 24 hours.

   Plasma aliquot B samples will remain stored at the Clinical Study Unit as a backup in a GLP-compliant freezer at -70°C, until shipment is requested.

The surgeon will place oxymetazoline-soaked pledgets according to usual practice. Dr. Elmaraghy will make two different observations to assess the amount of bleeding and ease of hemostasis (10)

1) A four point scale to record subjective bleeding following removal of pledgets

0= none, 1= minimal/restricted, 2=moderate/diffuse ooze, 3=severe/brisk

2) A six point scale to assess ease of hemostasis
   1=very easy, 2=easy, 3=usual, 4=some effort required, 5=difficult, 6=extremely difficult

Blood pressure and heart rate and will be retrieved from EPIC for analysis

Prior to the study Drs. Cartabuke & Elmaraghy determined that 10 pledgets in 15 ml of oxymetazoline (1.5 ml per pledget) provided the necessary amount of oxymetazoline for clinical use. The number of pledgets placed will be recorded at the time of insertion. If placement is separated by greater than five minutes, then this will be recorded as a separate event. The volume at each time point and the total dose will be recorded. Age-matched, procedure matched control patients not receiving oxymetazoline will be used for comparison. We will do a retrospective chart review of the control patients for hemodynamic parameters.

Statistical Analysis:

Compare the incidence of hypertension using systolic blood pressure and mean arterial pressure criteria using age adjusted normative tables

Compare the incidence of bradycardia defined as HR < 60 bpm, or tachycardia defined as HR>100

Compare the use of vasodilators for the treatment of hypertension

Compare the use of atropine/glycopyrrolate for the treatment of bradycardia

Compare the volume of oxymetazoline instillation and hemodynamic changes

Measure the serum level of oxymetazoline at approximately 5 (3-6 min), 10(8-12 min), 20(18-22 min), 45 (30-60 min), 90 (75-120 min) and 150 (135-240 min) minutes using the protocol specified above.

Compare the degree of bleeding and the ease of hemostasis using the subjective rating scale by the single surgeon observer.

All demographic and parametric data will be presented as mean (±SD). Normally distributed interval data will be analyzed using unpaired t-test. Nominal or ordinal data will be analyzed using Chi-quared contingency table or a Fisher's exact test with Yates correction factor. A $P<0.05$ will be used to express statistical significance.

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