

**PHASE 2 RANDOMIZED CONTROL TRIAL OF ARGININE THERAPY FOR PEDIATRIC
SICKLE CELL DISEASE PAIN**

NCT02536170

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IRB00076988

**Emory University and Children's Healthcare of Atlanta
Consent to be a Research Subject and HIPAA Authorization**

Title: Phase 2 Randomized Control Trial of Arginine Therapy for Pediatric Sickle Cell Disease Pain

Principal Investigator: Claudia R Morris, MD, Division of Pediatric Emergency Medicine

Investigator-Sponsor: **Claudia R Morris, MD, Division of Pediatric Emergency Medicine**

If you are the legal guardian of a child who is being asked to participate, the term "you" used in this consent refers to your child

Introduction

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide to consent (agree) to be in the study or not to be in the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

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 may search this Web site at any time.

Study Overview

Arginine is a simple amino acid that is found in many foods and is part of the proteins in your body. Patients with sickle cell disease have low levels of the amino acid arginine and these low levels may be related to pain episodes. Increasing levels of arginine in the blood may lower pain and/or lower the amount of pain medication (like morphine) that is needed to treat your pain. It may also decrease the amount of time spent in the hospital. The aim of this study is to determine whether giving extra arginine to patients with sickle cell disease seeking treatment for a pain crisis (vaso-occlusive painful events (VOE) will decrease pain scores, decrease the need for pain medications or decrease length of hospital stay or emergency department visit. However, arginine is not FDA approved for this use but we think it can be helpful when taken during a pain crisis. We want to learn whether this drug helps children who are having a pain crisis. If this study shows that it is effective for these patients, then it may improve how doctors treat sickle cell patients in a pain crisis.

Procedures

Approximately 150 participants will take part in this study at Children's Healthcare of Atlanta.

If you agree to participate in this study, your participation will last until you are discharged from the hospital and consist of the following:

- You will be asked a screening history and receive a physical exam (this includes a pregnancy test for girls 12 years and older)
- You will be asked to give blood samples from your IV or a butterfly catheter will be placed. We will make every effort to collect the blood sample at the time of routine blood draws whenever possible. We will collect about 1-2 tablespoons at the following time points:
 - Before study drug is received
 - Within the first 24 hours if admitted to the hospital.
 - On day 7 if admitted that long, and prior to discharge
- You will be asked to breathe into a tube around the same time of your study blood draw and every day of hospitalization (to look at nitric oxide - a test for inflammation in their breath).
- You will provide a daily urine sample on the days of the study blood draws.
- You will be randomly assigned to one of the following groups. This means that you have an equal chance of receiving any of the medications or doses listed below:
 - Arm 1: Standard dose (100mg/kg) IV infusion 3 times a day until IV discontinued or discharged
 - Arm 2: A one-time loading dose (200mg/kg) followed by the standard dose (100mg/kg)IV infusion 3 times a day until IV discontinued or discharged
 - Arm 3: Placebo (normal saline 1-2 ml/kg) IV infusion 3 times a day until IV discontinued or discharged
- You will be asked questions by the study staff or your doctor about your symptoms daily along with the usual pain score questions and fill out a questionnaire about your pain symptoms.
- You will have a sticky sensor gently secured to your forehead and/or arm or leg to look at blood flowing to your brain or painful arm/leg and blood flow to the arm or leg that doesn't hurt before study drug is delivered, and then after study drug is delivered, for up to 2 hours on the first day, and then for 5-10 minutes daily (20 minutes max), when staff is available. A blood pressure sensor will be secured to your upper arm and fore finger during this time.
- We will look in your medical chart for information related to your health and this study and also to see if you returned to the ED for up to 30 days after going home.

Risks and Discomforts

Arginine both orally and through the IV is safe and usually well tolerated. Allergic reaction is a risk with any medication, but no serious reaction to arginine has been reported when it is used in proper doses. You may experience common side effects such as flushing, headache and nausea intravenous arginine. There is always a risk of fainting when blood is drawn or development of an infection from the blood draw. You may experience a rare side effect known as priapism (when an erect penis does not return to its normal state). This is a rare side effect has not yet been reported but possible since nitric oxide is possibly involved in this mechanism. The sticky sensor on your forehead or arm/leg to measure blood flow does not hurt but you can ask to have it removed at any time. The only possible discomfort for children with sensitive skin is minor temporary skin irritation from contact with the rubber optical sensor on the forehead or arm/leg. The light used to make the measurements of blood flow in the brain is very low in power and is considered to present minimal risk-that is, no more risk than you would encounter in everyday life. There is no known risk for this procedure. The energy of the light is well below American National Standards Institute (ANSI) light levels and in compliance with the United States Food and Drug Administration (FDA). The energy of the light used in this test is many times less than energy you would receive from the sun on an outdoor walk on a sunny day.

If you are a female >11 years old: to protect against possible side effects of the study drug, women who are pregnant or nursing a child may not take part in this study. All females older than 11 years will receive a pregnancy test prior to randomization or receiving the study drug

New Information

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Benefits

If you receive arginine, you may have less pain during your current pain crisis, may require less pain medication, and may have a shorter hospital stay, or there may be no direct benefit to you from participating in this study. This trial may lead to a new treatment for pain in sickle cell disease, and may also lead to future studies using arginine therapy to treat painful events. If this study provides a new treatment for pain, it may help all sickle cell disease patients in the future.

Compensation

You will get \$30 for the first day you participate in all study requirements and another \$30 on the day of discharge if all study requirements and discharge bloodwork is obtained. If you do not finish the study, you will be paid for the days you have participated. You will receive a total of \$60, if you participate in all study visits.

Other Treatment Outside this Study

If you decide not to enter this study, there is care available to you outside of this research. You do not have to be in this study to be treated for sickle cell disease.

Confidentiality

Emory and Children's Healthcare of Atlanta at Hughes Spalding, Egleston and Scottish Rite will keep any research records that it creates private to the extent that this is required to do so by law. Whenever possible, a study number, rather than your name, will be used on study records. Your name and other identifying information will not appear when we present or publish the study results.

Study records can be opened by court order. They also may be provided in response to a subpoena or a request for the production of documents.

Medical Record

If you are or have been a Children's Healthcare patient, you have a Children's Healthcare medical record. Copies of the consent form/HIPAA authorization that you sign will be put in your Children's Healthcare medical record.

Results from standard of care test and labs will be documented in your Children's Healthcare medical record; however the results of research study tests or procedures will not be put in your Children's Healthcare medical record. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA privacy rule. State and federal laws may not protect the research information from disclosure.

Children's Healthcare does not control results from tests and procedures done at other places, so these results will not be placed in your Children's Healthcare medical record. They will likely not be available to Children's Healthcare to help take care of you. Children's do not have control over any other medical records that you may have with other healthcare providers. Children's Healthcare will not send any test or procedure results from the study to these providers. If you decide to be in this study, it is up to you to let your health providers know.

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the

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Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the “Privacy Rules.” Here we let you know how we will use and disclose your PHI for the study.

PHI that will be Used/Disclosed:

The PHI that we will use and/or disclose (share) for the research study includes

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results.

Purposes for which your PHI will be Used/Disclosed:

We will use and disclose your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information.

Use and Disclosure of Your Information that is Required by Law:

We will use and disclose your PHI when we are required to do so by law. This includes laws that require use to report child abuse or abuse of elder or disabled adults. We will also comply with legal requests or orders that require us to disclose your PHI. These include subpoenas or court orders.

Authorization to Use PHI is Required to Participate:

By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form to authorize the use and disclosure of your PHI. If you do not authorize the use and disclosure of your PHI for the study, then you may not participate in the research study or receive research-related treatment. You may still receive non-research related treatment.

People that will Use and/or Disclose Your PHI:

The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.
- Emory, Grady Health System and Children’s Healthcare may use and disclose your PHI to get payment for study related treatment and to run normal business operations.
- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- The Principal Investigator, Claudia Morris, MD, is the Sponsor of the study. The Sponsor may use and disclose your PHI to make sure the research is done correctly and to collect and analyze the results of the research. The Sponsor may disclose your PHI to other people and groups like study monitors to help conduct the study or to provide oversight for the study.
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
 - Emory offices that are part of the Human Research Participant Protection Program and those that involved in study administration and billing. These include the Emory IRB, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research.
 - Children’s Healthcare offices and Grady Health System involved in the study administration and billing.
 - Government agencies that regulate the research including: [Office for Human Research Protections; Food and Drug Administration; Veterans Administration].

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- Public health agencies.
- Research monitors and reviewer.
- Accreditation agencies.

Expiration of Your Authorization

This authorization will not expire because it is a research study.

Revoking Your Authorization

If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must write to: Dr. Claudia Morris [REDACTED]

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure that the study was done properly and the data is correct. If you revoke your authorization you will not be able to stay in the study.

Other Items You Should Know

Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers or health care clearinghouses. If we disclose your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations and/or for other purposes besides this study.

In Case of Injury

If you get ill or injured from being in the study, Emory, Grady Health System and Children's Healthcare of Atlanta would help you to get medical treatment. Emory, Grady Health System Children's Healthcare of Atlanta, and the sponsor have not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is proved that your injury or illness is directly caused by the negligence of an Emory, Grady Health system or Children's Healthcare of Atlanta, or sponsor employee. "Negligence" is the failure to follow a standard duty of care.

If you become ill or injured from being in this study, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs.

If you believe you have become ill or injured from this research, you should contact Dr. Morris [REDACTED]. You should also let any health care provider who treats you know that you are in a research study.

Costs

There will be no costs to you for participating in this study, other than basic expenses like transportation. You will not be charged for any of the research activities.

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Withdrawal from the Study

You have the right to leave a study at any time without penalty. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

The researchers and the US Food and Drug Administration also have the right to stop your participation in this study without your consent if:

- They believe it is in your best interest;
- You were to object to any future changes that may be made in the study plan;
- or for any other reason.

Contact Information

Contact Dr. Claudia Morris, MD [REDACTED]

if you have any questions about this study or your part in it,

- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board [REDACTED]

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a [REDACTED].

If you are a patient receiving care from Grady Health System and you have a question about your rights, you may contact the [REDACTED]

Children’s Healthcare of Atlanta at Hughes Spalding is owned by the Fulton-DeKalb Hospital Authority (FDHA) and managed by HSOC, INC., an affiliate of Children’s. The FDHA maintains oversight for the Grady Health System. If you are a patient receiving care at Children’s Healthcare of Atlanta at Hughes Spalding and have a question about your rights, please contact Kristine Rogers, [REDACTED]

If you are a patient receiving care at Children’s Healthcare of Atlanta (other than Hughes Spalding) and have a question about your rights, please contact Kristine Rogers, [REDACTED]

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Consent

Please print your name and sign below if you agree to be in this study. By signing this consent form, you will not give up any of your legal rights. We will give you a copy of the signed consent to keep.

Name of Subject

Signature of Subject

Date

Time

Signature of Person Conducting Informed Consent Discussion

Date

Time

Name of Person Conducting Informed Consent Discussion

Signature of Legally Authorized Representative

Date

Time

Authority of Legally Authorized Representative or Relationship to Subject