Protection of Human Subjects

An example shared by Claudia Morris, MD

The proposed clinical trial meets the definition of Human Subjects research.

Considerations for the Protection of Human Subjects

A. Human Subjects Involvement, Characteristics and Design

Human subjects, mainly African American children 3- 21 years old with a diagnosis of sickle cell disease (SCD) presenting to an emergency department or clinic with a vaso-occlusive pain and a pain score ≥ 5/10 seeking treatment for acute pain will be eligible for this study. The Aflac Sickle Cell Center at Children's Healthcare of Atlanta (CHOA) provides care to a large population of > 1600 children with SCD followed regularly at the comprehensive sickle cell clinic. Nationally, SCD is a disease seen primarily in the African-American population, although a growing Hispanic population is also affected. SCD affects both male and female patients equally. The population of SCD at the CHOA is mainly African-American and equally represented by both genders. There is no reason to assume differences in outcomes according to gender or ethnicity. Although equal recruitment of both males and females will be attempted, all data will be analyzed together. Also, non-African American SCD patients who meet eligibility criteria will be included in the study and every attempt will be made to recruit these patients.

1. Patients will be recruited from the ED, clinic and day hospital. Blood, exhaled breath for nitric oxide, a urine sample and medical data will be obtained on patients enrolled. A pain score will be obtained in the ED and daily during admission. Blood and other samples will be collected specifically for this study but we will use existing and future medical records and medical history information. All consenting patients will undergo phlebotomy and intravenous (IV) catheter placement (which is standard care for SCD and VOE in an ED). Daily samples of urine and nitric oxide in exhaled breath will be obtained during hospitalization and blood will be obtained on day 1 and at discharge. Blood samples for this study will be drawn at the time of other phlebotomies whenever possible to limit discomfort to the patient. Discomfort from venipuncture will be experienced, and bruising from the blood draws are a potential risk to the patient.

2. Patients with SCD and VOE meeting entry criteria will be approached concerning entrance into the clinical trial. A study coordinator or investigator will explain the study to the patients and their families and will obtain consent on all patients. Patients and/or parents will sign an IRB-approved consent form. Patients are free to exit the study at any point. Patients will receive all standard therapy for their SCD and pain even if they do not participate in this study. Those randomized into the trial will receive the standard IV arginine (100 mg/kg/dose TID), or an initial loading dose (200 mg/kg X 1) followed by the standard dose or placebo three times a day until discharge.

B. Sources of Materials

HOW SAMPLES/SPECIMENS/DATA WILL BE STORED
Blood, exhaled breathe, and medical data will be collected on patients enrolled. Blood and exhaled breathe will be collected specifically for this study but we will use existing medical records for past medical history information. Only the PI, collaborators and the study coordinator will have access to identifiable information. Samples will have de-identified study numbers to ensure subject confidentiality, and patient information will be stored in a database that is password-protected. The study lap-top will be stored in a locked cabinet in a locked office. All medical and research information will be kept in secured computer files at the sites. Unique subject identifiers will be used to label all data and research samples. With regard to subject safety and protection, the following necessary precautions will be taken: first, all information collected or discovered will be kept confidential, accessible only to authorized study investigators. No potential individual identifiers will be used in any reports or publications. Access to research samples will be limited using either a locked room or a locked freezer. Samples and data will be stored using codes assigned by the investigators or their designee(s).

HOW SAMPLES/SPECIMENS/DATA WILL BE TRACKED
Samples will be tracked by logging them into a database containing sample number, date received and location of storage. If samples are sent to collaborators, this will also be entered into the database.

WHAT WILL HAPPEN TO THE SAMPLES/SPECIMENS/DATA AT THE COMPLETION OF THE PROTOCOL? At the completion of the protocol (termination), samples and data will either be destroyed after final analysis, or after IRB approval, maintained in an approved repository established in the protocol.

C. Potential Risks

The risks in this study are considered low. All consented patients will undergo phlebotomy and IV placement. Patients admitted to the floor may undergo 2 additional study blood draws before discharge. Blood samples for this study will be drawn at the time of other phlebotomies whenever possible to limit discomfort to the patient. Discomfort from venipuncture will be experienced, and bruising from the blood draws are a potential risk to the patient.

For patients randomized into the clinical trial, the risks of the study are confined to those associated with the arginine administration. As with any food or medication, the risk of an allergic reaction is a small but possible complication. Arginine is a nutritional supplement with a low toxicity and has been safely used in many human studies, including a number of studies in both adults and children with SCD. Intravenous arginine is preferred over oral due to mild stomach discomfort may be experienced at higher doses, and issues with compliance with respect to ingesting a large number of pills. Intravenous arginine may cause flushing or headache. Patients with compromised liver or kidney functions will be excluded from participation. Priapism is also a theoretical toxicity of increased nitric oxide production in male participants, as nitric oxide is an important component in erection physiology. However in our experience, anecdotally arginine rapidly treated priapism in one case report at CHRCO. An overdose of L-arginine hydrochloride can cause acidosis. All patients enrolled in the study will also receive treatment for vaso-occlusive pain episodes that has been standardized across all participating sites, based on

clinical practice guidelines and the expertise of hematology and emergency medicine specialists with vast sickle cell clinical experience.

Adequacy of Protection Against Risks

A. Subject Recruitment and Informed Consent

Eligible patients will be approached by the principal investigator or co-investigators/study coordinator and recruited for the study. Consent procedures will follow the rules and regulations of the Institutional Review Board whose approval will be obtained before the start of the study. Each volunteer subject will receive an oral and written explanation of the purposes, procedures, and risks of this study. A copy of the signed consent form will be placed in the medical record. A member of the protocol team will be available to answer questions about the study to be performed. All risks from the study (see above) will be anticipated and precautions initiated to detect or prevent complications. Both hematology and emergency medicine clinical support is available to patients in this study. A Data and Safety Monitoring Board will be established for the clinical trial.

B. Protection Against Risk

Additional protections for children involved as subjects in research will be applied according to the code of federal regulations established by the Department of Health and Human Services. A Data Safey Monitoring Board will be established at CHOA (See details below). If there is an injury related to this study, the study PI Dr. Claudia R. Morris MD will be notified immediately and the patient will receive appropriate medical attention.
Patients may ask any questions about the study and may withdraw their consent at any time. Patients may decide not to participate in this study and will still received standard treatment for their SCD.

Potential Benefits of the Proposed Research to Participants and Others

Children who are enrolled in the VOE study may receive benefit from the study treatment they are receiving, or they may receive no benefit from this treatment (if they receive placebo, or the treatment does not improve pain). However, as a safe, nontoxic dietary supplement, arginine has already demonstrated the ability to decrease total opioid use and pain scores in a single-center randomized controlled trial. Arginine therapy may prove beneficial for SCD patients by resulting in an increase in NO production, reversing vasoconstriction and is potentially a new therapy for the treatment of pain in children with SCD. Global arginine bioavailability will also be investigated as a potential biomarker of VOE severity and admission. An objective biomarker of pain severity would be a clinically useful tool. The outcome of this study may significantly impact SCD by providing insight into mechanisms of vaso-occlusive pain. If valuable information about SCD results from this research then patients with SCD may receive benefit in the future from this knowledge. Finally this study may improve sickle cell care in general by increasing knowledge about SCD and pain in the emergency medicine arena.

The benefits of this study may impact significantly on the SCD population as a whole.
There are minimal risks associated with participation in this study. Therefore the risks to subjects are reasonable in relationship to the anticipated benefits.

Importance of the Knowledge to be Gained

The risk/benefit ratio in this study is acceptable because of the potential benefit to all SCD patients experiencing pain. Patients have very little risk from participating in this study (i.e. phlebotomy, minimal risks of arginine therapy) but the gains could be substantial in identifying a novel therapy for VOE and/or biomarker of VOE severity that may change clinical practice. Over 200,000 visits to an emergency department for SCD-related complications occur annually, the majority of which are related to pain. Novel therapies for this common and debilitating complication of SCD are needed. This study will add to our understanding of mechanisms of pain, and may lead to a decrease in pain and suffering for patients with SCD.

Data and Safety Monitoring Plan/Board

Not applicable to this study.