Title: Does IV Acetaminophen Reduce Opioid Requirement in Pediatric Emergency Department Patients with Acute Sickle Cell Crises?

Location: Newark Beth Israel Medical Center

Principal Investigator: Cena Tejani, M.D.

Co-Investigator: Tina Dhebaria, D.O.

Division: Pediatric Emergency Department

Sponsors: None

Abstract:
Background: Intravenous (IV) acetaminophen has been available and widely used in European countries for the management of pain. In 2010, IV acetaminophen was FDA-approved for the management of pain in the United States. Manufacturer labeling for IV acetaminophen states that it can be used for "moderate to severe pain with adjunctive opioid analgesics in adults and children 2 years and older." There are very few studies assessing the use of IV acetaminophen in the management of pain in pediatrics. Several studies have implemented IV acetaminophen for post-operative pain and low back pain and demonstrated an opioid-sparing effect. To date, there are no published studies assessing the use of IV acetaminophen in sickle cell crisis pain. Standard treatment currently involves oral analgesics including acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and narcotics. Management in the Pediatric Emergency Department (PED) involves either intranasal opioids or parenteral (IV) ketorolac and opioids. Although pain control is extremely important for these patients, the misuse and addiction caused by prescription and IV opioid medications has become a public health issue.

Methods: This is a single-center, prospective, randomized, double-blinded, controlled study in an academic urban pediatric emergency department of children with sickle cell disease presenting with acute sickle cell crisis pain between ages of 4 to 16 years, with a pain score of 6/10 or higher on the Wong-Baker modified FACES pain scale. In order to detect a difference of 0.2 mg/kg in cumulative dosage of morphine (at our institution, 0.3 mg/kg morphine deems an inpatient admission for parenteral pain management) with 80% power and alpha of 0.05, we calculated a sample size of 33 patients in each group. All patients will receive IV ketorolac and IV morphine. Patients will be randomized to receive IV acetaminophen or IV saline (volume-equivalent). Pain scores will be obtained at baseline, and again at 30 minutes, 60 minutes, 90 minutes, and 120 minutes after medication administration. Cumulative morphine dosing, rates of admission, and rates of adverse effects of morphine will also be analyzed. Our primary objective is to decrease the need for subsequent opioid administration. Our secondary objectives are to determine if IV Acetaminophen decreases pain score at 30 minutes, 60 minutes, 90 minutes, and 120 minutes, decreases the rate of admissions, and decreases the rate of adverse effects from opioids.

Participant Selection: Patients with sickle cell disease (sickle cell SS, sickle cell SC, and sickle cell beta-o-thalassemia) ages 4-16 years will be recruited from Newark Beth Israel Pediatric Emergency room that meet eligibility criteria, including a pain score of 6/10 or higher on the Wong-Baker modified FACES pain scale. Through randomization, all eligible patients will be assigned a study participant number.

Sample size: In order to detect a difference of 0.2 mg/kg in cumulative dosage of morphine (at our institution, 0.3 mg/kg morphine deems an inpatient admission for parenteral pain management) with 80% power and alpha of 0.05, we calculated a sample size of 33 patients in each group.

A. Purpose of Study:

The purpose of our study is to determine whether IV acetaminophen can decrease the need for subsequent opioid administration in the acute management of sickle cell crisis pain in the pediatric emergency room.

B. Background:

According to the Expert Panel guidelines on Sickle Cell Disease (SCD), more than 2 million Americans are either homozygous or heterozygotes for the sickle cell mutation. Of those 2 million, it is estimated that approximately 75,000 to 100,000 have homozygous sickle cell disease (HbSS)[1]. Every year, newborn screening identifies about 2,000 newborns with SCD making sickle cell disease one of the most prevalent genetic disorders in the United States [2]. Sickle cell disease continues to remain an economic burden in the United States. In a period of four years, approximately 75,000 hospitalizations occurred to due to SCD, costing approximately $475 million [3]. In 2004 alone, there were 113,000 hospitalizations related to SCD, costing about $488 million [4]. In 2005, cost of medical care provided to children with SCD covered by Medicaid averaged to $11,702 and $14,772 for those with employer-sponsored insurance [5]. Average lifetime cost of SCD is approximately $460,000 [6].

Vaso-occlusive crisis pain (VOC) is the most common complication and the most common cause of morbidity and indication for hospital admission in this population [1,7]. It accounts for up to 90% of emergency room visits [8,9]. There is no definitive standard therapy for treatment of acute VOC, however many approaches have been identified [10]. Treatment currently involves rest, rehydration, oral and IV analgesics including acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and narcotics [11]. Although pain control is extremely important for these patients, the misuse and addiction caused by prescription and IV opioid medications has become a public health issue. Approximately 53% of emergency room physicians and 23% of hematologists feel that more than 20% of patients with sickle cell disease are addicted to opioids [12]. More research is needed to allow optimal pain relief in children with painful crises, while decreasing the addiction potential to opioid medications.

Intravenous acetaminophen has been available for over 20 years, and is widely used, in European countries for the management of pain. It has been described to provide fast and significant pain relief, while demonstrating an opioid-sparing effect [13]. In 2010, IV acetaminophen was FDA-approved for the management of pain in the United States [14]. Manufacturer labeling for IV acetaminophen states that it can be used for "moderate to severe pain with adjunctive opioid

analgesics in adults and children 2 years and older. " [15] There are, however, few studies assessing the use of intravenous (IV) acetaminophen in the acute management of pain, in both adult and pediatrics. Several studies implementing IV acetaminophen for post-operative pain management and low back pain have demonstrated an opioid-sparing effect [13, 16]. Hong et al demonstrated reduced fentanyl consumption in pediatric patients after inguinal hernia repair after being administered combined IV ketorolac and acetaminophen [17].

To date, there are no published studies assessing the use of IV acetaminophen in sickle cell crisis pain. Our study looks to determine if the use of IV acetaminophen can provide adequate pain control and ultimately demonstrate an opioid-sparing effect in patients treated for sickle cell pain crisis in the Pediatric Emergency Department. We also aim to determine if there is a subsequent decrease in the rate of admissions, overall decrease in pain scores, and decrease in dose-related adverse effects from opioids.

C. Description of Methodology:
Prospective randomized, double-blinded, controlled study in an academic urban pediatric emergency department of children with sickle cell disease presenting with acute sickle cell crisis pain between ages of 4 to 16 years, with a pain score of 6/10 or higher on the Wong-Baker modified FACES pain scale.

Sample size: In order to detect a clinical difference of 0.2 mg/kg in cumulative dosage of morphine (at our institution, 0.3 mg/kg morphine deems an inpatient admission for parenteral pain management) with 80% power and alpha of 0.05, we calculated a sample size of 33 patients in each group.

Data will be collected from the electronic health record (EHR) and transcribed into a password-protected de-identified database to which only the PI and Co-Investigators will have access.

Duration of the study is expected to be 2 years.

D. Participant Selection: Patients with sickle cell disease (sickle cell SS, sickle cell SC, and sickle cell beta-o-thalassemia) ages 4-16 years will be recruited from Newark Beth Israel Pediatric Emergency room that meet eligibility criteria, including a pain score of 6/10 or higher on the Wong-Baker modified FACES pain scale. Through randomization, all eligible patients will be assigned a study participant number.

Eligibility:
Any patient ages 4-16 years with sickle cell disease, whose symptoms are consistent with sickle cell crisis pain, with a pain score of 6/10 or higher on the Wong-Baker modified FACES pain scale.

Exclusion criteria:
- Patient with fever (38C or 100.4F)
- Patient less than age 4 years
- Patient greater than 16 years
- Patient with hypersensitivity/allergy to either morphine, NSAIDs, or acetaminophen

- Patient received acetaminophen within the past 4 hours
- Patient received an NSAID within the past 6 hours
- Patient with known liver disease or renal disease
- Patient receiving intranasal opioid therapy
- Patient not requiring IV morphine
- Patient enrolled in the study within the past 30 days

E. Description of Agents Involved:

The investigational agent that will be used in this study is intravenous acetaminophen, which is an anti-pyretic and analgesic medication. It is currently FDA-approved for use in "management of mild to moderate pain in adult and pediatric patients 2 years and older, the management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older, and the reduction of fever in adult and pediatric patients [15]."

It will be given as a one-time dose of 15 mg/kg with max dose of 1,000 mg in the initial management of sickle cell crisis pain.

F. Description of Procedures involved:

The total number of required patients will be 33 per arm (66 patients total). The targeted study population is patients with sickle cell disease who are between the ages of 4-16 years presenting with acute sickle cell crisis pain. The expected duration of the study is 2 years.
Prior to initiation of study, the researchers will be responsible for the randomization process. The goal of this study is to enroll 66 patients total (33 per arm). Patients will be randomly assigned to a study arm via an online randomization process. A primary master list will be provided to the pharmacy to maintain blinding of the recruiting and treating physicians as well as the nurses administering the medications. Only the pharmacy staff will have knowledge of which medication the patient will be receiving. A secondary list will be kept in a locked and secured cabinet in the Pediatric Emergency room, to which only the primary and secondary investigator will have access in emergency circumstances.

Detailed study procedures:

Study investigators/ED physicians will identify potential candidates via chief complaints or visit reasons of sickle cell via the Emergency Department's tracking board.

Potentially eligible patients are screened with inclusion/exclusion criteria.

If patients are eligible, study investigators and/or attending physicians or fellows will obtain informed consent and explain potential risks and benefits with receiving study interventions.

Patients will receive standard therapy plus either intervention medication or placebo (normal saline). All patients and their family members will be blinded to whether the patient is receiving acetaminophen or saline. All patients will receive conventional standard therapy (ketorolac and morphine), which will be ordered by the emergency department resident, fellow, or attending. Arm A will receive 15 mg/kg IVP bolus of acetaminophen in addition to ketorolac and morphine. Arm B will

receive ketorolac, morphine, and normal saline placebo (volume-equivalent) to maintain blinding of the study subjects.

The emergency department resident, fellow, or attending, or a study investigator who is a physician, will place an order for the study medication. This order will be placed as a non-formulary medication, with both the dose of IV acetaminophen and its volume equivalence, with the study protocol number and participant number (ie: 1000 mg acetaminophen/100 mL; protocol # XYZ, participant #1). This is to ensure the patient receives the correct dose or volume equivalent of the medication to which they are assigned.

Upon receiving the order, the pharmacy staff will confirm which arm the patient is assigned to based off the participant number. They will then verify the dose of acetaminophen or the volume of placebo is correct. The pharmacy staff will then prepare the medication. The nurse assigned to the patient will administer the intervention (acetaminophen) or placebo (normal saline). Prior to administration, all medication labeling will be obscured to maintain blinding of the patient, their family members, nurses, and physicians.

The ED physician (resident, fellow, or attending) will approach the patient to obtain a pain score at designated time intervals. The data will be recorded in the electronic health record (EHR). If the patient requests additional medication, the orders will be placed by the medical resident or attending that are assigned to the patient in the ED.

All data retrieved from the EHR will be transcribed into an encrypted and password protected electronic database by the study investigators.

All patient identifiers will be de-identified in the database. All participants will be assigned a study participant number. This database will be stored in the Emergency Department faculty or research room. Only the study investigators will have access to the electronic database.

At the end of study enrollment, the data will be analyzed.

At the conclusion of the study, the final results and conclusions will be presented to the IRB. All data recorded on electronic databases will be deleted.

G. Potential Risks or Adverse Events:

The most common associated adverse reactions reported in pediatrics include nausea, vomiting, constipation, and pruritus. Potential serious risks involved include hepatic injury, serious skin reactions, allergy, and hypersensitivity. In the event any of these events occur, the medication will be discontinued immediately (if still being administered), or appropriate supportive care will be initiated if occurs after administration is complete.

H. Potential Benefits:

Potential benefits of this medication are better pain control with fewer side effects than seen with opioids.

I. Questionnaires and Survey Instruments:
None.

INVESTIGATOR QUALIFICATIONS AND EXPERIENCE: see attached CVs

SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT/ASSENT
Consent and procedure timeline/process
The pediatric EM attending, fellow, or resident caring for the patient will determine if the patient is eligible. If the patient is eligible, and has no criteria that would exclude them from the study, the parents will be asked to participate (see verbal consent script and documentation of verbal consent forms). Patients will be asked to participate solely based on inclusion/exclusion criteria. Consent will be obtained by the PEM attending physician or fellow.

Subject Comprehension
We will provide a verbal consent script to guarantee a standardized delivery of verbal consent. This will also maximize the patient's comprehension of the study, by using basic language that is easy to understand.

Costs and Compensation to Subjects
There will be no costs or compensation to subjects taking part in this study.

Potential Conflict of Interest and Funding
Funding for this study will be provided by internal departmental funds. No funds will accrue to any of the investigators. No funding is sought or exists from commercial sources. No relationship exists or is sought with any commercial company.

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