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Safety of Intravenous Arginine Therapy in Children with Sickle Cell Disease Hospitalized for Vaso-occlusive Pain: A Randomized Placebo-Controlled Trial in Progress

Loretta Z. Reyes, MD[1,2], **Janet Figueroa, MPH**[1,2], **Deborah Leake, NP**[2], **Kirshma Khemani, MD**[1,2], **Polly Kumari, MBBS**[1,2], **Nitya Bakshi, MD**[1,2], **Peter A. Lane, MD**[1,2], **Carlton Dampier, MD**[1,2], **Claudia R. Morris, MD**[1,2]

[1.]Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA

[2.]Children's Healthcare of Atlanta, Atlanta, Georgia, USA

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To the Editor:

Sickle cell disease (SCD) is the most common hemoglobinopathy in the United States and vaso-occlusive pain episodes (VOE) are the leading cause of hospitalizations and emergency department (ED) visits[1]. There are limited therapies for acute management of VOE that directly target the underlying etiology for sickle-related pain therefore treatment is largely symptomatic. Moderate-to-severe pain is typically treated with parenteral hydration, opioids, and hospitalization to achieve adequate pain control.

Arginine is a conditionally essential amino acid and the obligate substrate for nitric oxide (NO) synthesis. NO is a potent vasodilator which is essential for vascular homeostasis; low NO bioavailability contributes to sickle cell vasculopathy. SCD is an "arginine deficiency syndrome", where low arginine bioavailability correlates with pulmonary hypertension risk, early mortality, and pain severity, predicting the need for pediatric hospitalization[2, 3]. Arginine is also a precursor for kyotorphin (L-tyrosyl-L-arginine), an endogenous analgesic dipeptide[4]. Intravenous arginine therapy reduced opioid use by over 54% and significantly decreased pain scores in children hospitalized with SCD-VOE compared to placebo in a phase-2 randomized, double-blinded, placebo-controlled trial (RCT)[5]. A recent RCT of oral arginine therapy in children hospitalized for SCD-VOE in Nigeria similarly found a

Corresponding author: Dr. Loretta Z. Reyes, MD, Assistant Professor, Division of Pediatric Nephrology, Emory University School of Medicine, Atlanta, Georgia, USA, Children's Healthcare of Atlanta, Atlanta, Georgia, USA, loretta.reyes@emory.edu.

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reduction in total analgesia, pain scores, time-to-crisis-resolution, and total length of hospital stay[4].

IV Arginine has an excellent safety profile, having received FDA approval for growth hormone stimulation testing in 1973, utilizing 500 mg/kg/dose (maximum 30 grams/dose) over 30 min. IV Arginine also has been used in the management of mitochondrial diseases and sepsis with few side effects[6]. Adverse events (AEs) reported with IV Arginine use include nausea, vomiting, headaches, flushing, dyspnea, and dose-dependent effects on blood pressure, electrolytes (e.g., potassium) and acid-base imbalance. Thus, it is important to determine whether IV arginine might increase the frequency or severity of these events during VOE. A phase-2 RCT evaluating two IV Arginine dosing regimens at Emory/Children's Healthcare of Atlanta has recently completely subject enrollment. The objective of the current report is to review the safety of IV Arginine in this trial by examining rates of AEs and serious adverse events (SAE) after treatment across blinded study arms prior to locking the final data set for analysis of the primary and secondary end points.

This is a single-center, prospective, double-blind RCT studying the effects of IV Arginine therapy in children aged 3–21 years with SCD (any genotype), hospitalized for VOE and requiring parenteral opioids. Patients with hepatic or renal dysfunction (ALT>3 times normal upper limit, creatinine>1.0mg/dL respectively), new SCD-specific therapy (e.g., hydroxyurea, voxelotor) in last 3 months, Hgb<5g/dL, NO-based therapy in last month, or those previously enrolled were excluded from study participation. Patients were randomized within 24-hours of receiving their first dose of parenteral opioids in the ED into one of three IV Arginine treatment arms: A) standard dose (SD) (100 mg/kg/dose three times a day), B) loading dose (200 mg/kg/dose) followed by SD or C) placebo (IV normal saline 1–2 mL/kg three times a day).

Demographics, clinical characteristics, time-to-crisis-resolution, total parenteral opioid use, length of hospital stay, pain scores, blood biomarkers, and patient-reported outcomes were obtained before and after treatment. The primary outcome measure is total parenteral opioid use between study arms. Lab values above the upper limit of normal range were considered elevated and reported as AEs if present after enrollment.

The sample size calculated for this study was 108 patients (36 per arm), based on *Morris et. al, 2013*[5]. Chi-squared/fisher exact tests were utilized as indicated to compare development of AEs and SAEs across the randomization arms; a p-value<0.05 was considered significant. The study protocol is approved by Emory University and Children's Healthcare of Atlanta Institutional Review Boards, conducted under an active Investigational New Drug (IND) #66943 (*Sponsor-C.R.Morris*), registered with ClinicalTrials.gov (NCT02536170,) and is funded in part by FDA-R01FD004814-01A2 and NCCIH K24AT009893-01 (*to C.R.Morris*).

A total of 1548 patients were screened of which 266 were eligible with a guardian present; 114 were consented, 108 were randomized and 6 were categorized as screen failures (Supplemental Figure). The majority of patients (74%) were enrolled in the ED. The first patient was enrolled in March 2016; enrollment is now complete.

Patient demographics randomized by treatment group are provided in the Supplemental Table, which also includes a summary of the cumulative 372 AEs in 91 of 108 (84.3%) unique patients, and 28 SAEs in 19 (17.6%) unique patients; these are classified by system, and per treatment arm. There was a median of 2 AEs in patients who experienced AEs. Headache and gastrointestinal complaints including abdominal pain, nausea and vomiting were the most commonly reported symptoms and often occurred before administration of study drug; however, there were no significant differences across treatment arms in either the total AEs or in the AEs that occurred after initiation of treatment (Supplemental Table).

Multiple labs were monitored during the study and are documented in Table 1. Serum bilirubin, AST, and ALT (markers of liver function and hemolysis) were elevated at the time of randomization in some patients and increased after treatment, but there were no significant differences across treatment arms in total liver function AEs or in those that occurred after treatment. Although statistically significant differences among study arms were noted in serum BUN, serum bicarbonate and serum potassium, they were not clinically relevant (Table 1).

A cumulative total of 28 SAEs occurred in 19 of 108 unique subjects (17.6%); (2 SAEs occurred during a single prolonged hospitalization and 26 involved re-hospitalizations within 30 days); there was a median of 1 SAE per patient with any SAE, with a maximum of 5 SAE occurring in 1 patient. There were no SAEs “definitely related” to study drug administration, 9 SAEs were “possibly related” (re-hospitalization within 7 days) and the rest were “unlikely related” or “not related” to the study.

No differences in the seriousness ($p=0.208$), severity ($p=0.165$) or relatedness ($p=0.493$) for all events (SAEs and AEs), or those that occurred after treatment was identified across treatment arms.

This interim report on the safety of IV Arginine in children with SCD hospitalized with VOE reaffirms prior reports on the safety of IV Arginine therapy in this patient population[4–6]. IV Arginine therapy has been successfully used in the treatment of multiple medical conditions including mitochondrial encephalopathy with lactic acidosis and stroke like episodes (MELAS), acute metabolic strokes in primary mitochondrial disease (e.g., Kearns Sayre syndrome) and hyperammonemia crises due to urea cycle defects and improves mitochondrial function in SCD[6]. IV Arginine is administered as an Arginine-hydrochloride infusion, and it is generally well tolerated with minimal side effects. AEs reported in the literature with IV Arginine include changes in blood pressure, potassium, phosphate, acid-base status, and blood glucose, with pharmacokinetic studies reporting AEs related to the dose and rate of IV Arginine infusion.

As expected in a study of hospitalized patients with SCD, AEs were common, with a cumulative 372 AEs documented in 91 unique patients. Headaches and gastrointestinal complaints are established AEs associated with IV Arginine that were also observed in this study. These symptoms, which may be side effects of opioid use or may be features of VOE for some patients, were frequently present before patients received study drug, and there were no differences in AEs that occurred after treatment. No new AEs emerged compared

to what has previously been reported with arginine therapy. All SAEs were associated with re-hospitalization mainly for pain or ACS, or prolonged hospitalization. Less than 10% of patients were re-hospitalized at least once within 7 days of discharge, which is lower than published readmission rates of up to 20%[5]. No statistically significant differences in SAEs were found across study arms.

The results of this study are congruent with the available literature demonstrating no significant or clinically relevant changes in renal or liver function or changes in electrolytes or acid-base status with the administration of IV Arginine therapy. The observed mild decrease in serum bicarbonate did not result in acidosis, nor did any increase in serum potassium result in hyperkalemia. These findings are of clinical relevance since they could allow for less intensive lab monitoring during therapy and therefore reduce the need for multiple blood draws. Additionally, patients hospitalized for VOE typically receive NSAIDs as part of their analgesia regimen; the observation of a stable creatinine from admission to time of discharge likely means that IV Arginine will be well tolerated in patients receiving NSAID therapy.

Of particular interest in this study was the finding of elevated serum ALT levels in some patients before randomization that continued to rise during the course of the study. This was unlikely to be related to IV Arginine administration since it was observed in all 3 arms and may represent the course of liver dysfunction during VOE not previously described. Although this observation may not warrant any medical intervention, the presence of abnormal liver function tests may be of clinical importance in some patients hospitalized with VOE who often receive potentially hepatotoxic drugs like acetaminophen as part of their analgesia regimen.

To conclude, in this RCT of IV Arginine administration for the treatment of SCD patients hospitalized with VOEs, no unexpected SAEs occurred, and SAE/AE rates were similar across study arms. IV Arginine was generally well tolerated without the observation of new clinical or biochemical AEs compared to other arginine studies. This study provides further support for the safety of IV Arginine therapy in children with SCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Changes in lab values from pre-randomization to discharge (n=108 patients)

Lab value	Day 0	Day 1	Discharge	P-value for change over time
WBC	12.02 (8.35,15.82)	10.97 (7.75,13.72)	9.14 (6.42,11.45)	**<0.001**
Hgb, g/dL	9.2 (8,10.5)	8.35 (7.55,9.95)	8.2 (7.1,9.9)	**<0.001**
HCT	26.9 (24.4,30.5)	25.05 (22.65,28.25)	24.9 (21.7,28.4)	**<0.001**
Platelets	356 (222,458)	322.5 (190,428.5)	341.5 (226,465)	**<0.001**
Retic %	9.4 (4.9,14.1)	9.2 (5.8,13.9)	9.2 (4.6,13.3)	0.086
BUN	7 (5,9)	7 (5,10)	7 (5,10)	**0.020** **
Creatinine	0.5 (0.4,0.6)	0.5 (0.33,0.6)	0.43 (0.32,0.5)	0.084
AST *	42.5 (30,61)	41 (26,62)	38.5 (30.5,55.5)	0.257
ALT *	23 (19,33)	26 (19,40)	30.5 (21.5,54.5)	**<0.001**
Total bilirubin	1.9 (1.2,3.6)	1.8 (1.1,3.6)	1.7 (1,2.5)	**<0.001**
Sodium	138 (137,139)	138 (136,139)	138 (137,140)	0.070
Potassium	4 (3.7,4.2)	4.15 (3.7,4.4)	4.2 (3.9,4.5)	0.055 **
Chloride	106 (104,108)	107 (105,109)	107 (105,109)	**<0.001**
CO^2	25 (23,26)	25 (23,26)	25 (23,27)	0.515 **
Glucose *	97 (87,107)	100.5 (94,110)	96 (92,103)	0.167
Osmolality	283.9 (281.9,287.1)	283.7 (280.6,286.9)	284.1 (281.9,286.9)	0.136

Values shown median (25^{th}-75^{th})

Osmolality calculated via formula: 2(sodium) + glucose/18 + BUN/2.8

P-value: overall difference of lab values over time (from type 3 fixed effect for time from linear mixed model).

* Statistical tests were run on log-transformed due to non-normality; untransformed values are shown above.

** $p<0.05$ for statistically significant differences among study arms that are not clinically relevant