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Arginine Therapy for Sickle Cell Disease Acute Pain Episodes
The STArT Randomized Clinical Trial

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IMPORTANCE Acute pain episodes are the leading cause of emergency department visits and hospitalizations for patients with sickle cell disease (SCD), yet US Food and Drug Administration–approved drugs for acute pain episodes are lacking. During acute pain episodes, patients develop acute arginine deficiency associated with longer time to crisis resolution and greater total parenteral opioid use. Multiple single-center, phase 2 randomized clinical trials have shown that arginine is safe, is opioid sparing, improves cardiopulmonary function, and reduces length of hospital stay.

OBJECTIVE To determine the efficacy and safety of intravenous arginine for SCD acute pain episodes.

DESIGN, SETTING, AND PARTICIPANTS Prospective, phase 3, double-blind randomized clinical trial conducted between June 21, 2021, and June 13, 2024, in 10 US children's hospitals enrolling patients aged 3 to 21 years presenting to the emergency department with SCD acute pain episodes requiring parenteral opioids.

INTERVENTIONS Patients were randomized to receive intravenous arginine (200 mg/kg followed by 100 mg/kg every 8 hours until discharge; n = 129) or saline placebo (n = 142).

MAIN OUTCOMES AND MEASURES The primary outcome was time to crisis resolution, defined as hours from initial study drug delivery to last intravenous opioid dose. Secondary outcomes included total parenteral opioid use (intravenous morphine equivalents in milligrams per kilogram from first study drug dose to last intravenous opioid dose), pain scores, and patient-reported outcomes.

RESULTS Of 274 randomized participants, 271 received study drug; the mean age was 14.3 years (SD, 4.3 years), 51% were male, and 92% were Black. The trial was halted early for futility, as time to crisis resolution was similar in those receiving arginine vs placebo (median, 60.8 hours [IQR, 34.8-109.0 hours] vs 65.8 hours [IQR, 31.1-111.1 hours], respectively; absolute difference, 7.2 hours; 95% CI, −21.6 to 35.9 hours). No significant differences were seen in total parenteral opioid use, pain scores, patient-reported outcomes, or safety events.

CONCLUSIONS AND RELEVANCE Arginine therapy did not shorten time to crisis resolution compared with placebo among children and young adults with SCD acute pain episodes.

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Acute pain episodes among children with sickle cell disease (SCD) lead to more than 70 000 emergency department (ED) encounters each year in the US, with up to 70% of these encounters requiring hospitalization.[1-3] ED return visits following acute pain episodes encounters occur after as much as 29% of initial ED visits, while up to 28% of children hospitalized for acute pain episodes are readmitted within 30 days for another acute pain episode.[2] Despite the burden of SCD pain, US Food and Drug Administration (FDA)–approved drugs for acute pain are lacking.[4,5] Symptomatic treatment with opioid analgesics and nonsteroidal anti-inflammatory drugs has been the standard of care in EDs for decades,[6] with known potential adverse effects related to both. Effective treatments that target the underlying mechanisms of SCD acute pain episodes remain a significant unmet clinical need.

Arginine, a conditionally essential amino acid found in protein-rich foods,[7] is the obligate substrate for production of nitric oxide, a potent vasodilator that becomes depleted in SCD[8] and partially contributes to endothelial dysfunction and vasoconstrictive complications. Hemolysis triggers a global disruption of the arginine-nitric oxide pathway: cell-free hemoglobin released from lysed erythrocytes rapidly scavenges nitric oxide,[9] while erythrocyte-derived arginase metabolizes arginine to ornithine,[10] further reducing nitric oxide production and creating a hemolysis-associated arginine deficiency.[7] In addition to increased mortality risk,[10] low arginine bioavailability has been linked to need for hospitalization,[8] significantly longer time to crisis resolution, longer hospital length of stay, and higher intravenous opioid requirements during the inpatient stay in children with SCD pain.[4] Multiple randomized clinical trials (RCTs) in the US and abroad have established that arginine supplementation is safe, has opioid-sparing effects,[4,11,12] improves pain scores[11-13] and cardiopulmonary function,[13-16] and significantly decreases time to crisis resolution and length of stay compared with placebo.[12,13] Growing evidence supporting the use of arginine as an adjuvant treatment of SCD acute pain episodes led to its designation as an orphan drug by the FDA on May 8, 2024.

Given these promising findings, the Sickle Cell Disease Treatment With Arginine Therapy (STArT) trial, a phase 3 RCT, was conducted to assess the efficacy and safety of arginine therapy in this setting.

Key Points

Question Is intravenous arginine effective in reducing time to crisis resolution in sickle cell disease–related acute pain episodes?

Findings In this randomized clinical trial, halted early for futility, time to crisis resolution was not significantly different between the intravenous arginine and placebo groups (median, 60.8 hours vs 65.8 hours). Large variations in the primary outcome occurred among individuals and between study sites; no safety issues were identified.

Meaning Arginine therapy did not shorten time to crisis resolution compared with placebo among children and young adults with sickle cell disease–related acute pain episodes.

Methods

Study Design

We conducted a prospective, phase 3, multicenter, double-blind RCT to determine the efficacy and safety of intravenous arginine therapy compared with placebo in children and young adults with SCD acute pain episodes requiring parenteral opioids. This RCT was designed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The complete methodology of the STArT trial has been described previously, and details are available in the trial protocol in Supplement 1.[17] The STArT trial was conducted under an active FDA investigational new drug (No. 66943), included an independent data safety and monitoring board, and received approval from the University of Utah Institutional Review Board, which served as the single institutional review board of record. Participating sites relied on the single institutional review board. Written or electronic informed consent was obtained from all participants aged 18 years or older, and consent was obtained from a parent or legal guardian for all participants younger than 18 years; assent was obtained as required by each participating site.

Enrollment began in January 2021 with a goal of randomizing 360 participants over 5 years. Conditional power, under a range of plausible true effect sizes, was used to guide interim futility analyses. A conditional power of less than 20%, given the most liberal plausible effect size, was considered futile.

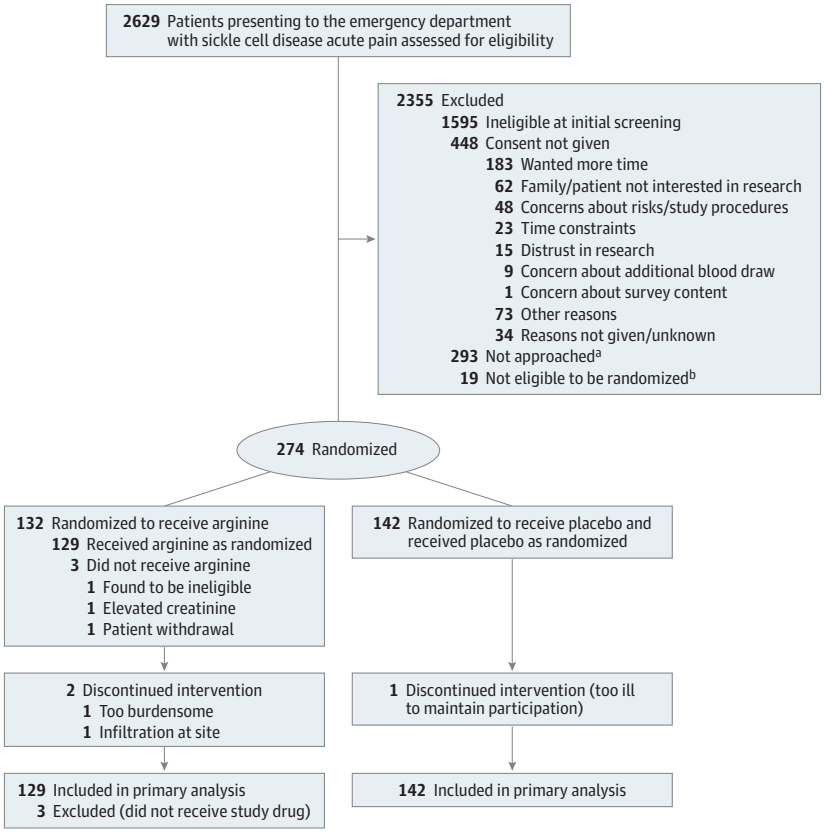
Setting and Participants

Ten US children's hospitals, 9 of which were Pediatric Emergency Care Applied Research Network (PECARN) sites (eTable 1 in Supplement 3), recruited patients aged 3 to 21 years with an established diagnosis of SCD (any genotype) who presented with acute pain requiring parenteral opioids for pain management. Inclusion criteria were intentionally defined broadly to maximize enrollment but led to a high number of screening failures, predominantly ED discharge after sufficiently responding to parenteral opioids. This strategy allowed the study team to gauge interest, rapidly obtain consent, notify the research pharmacy, and randomized eligible patients as soon as possible in the ED once an admission decision was made. Exclusion criteria were ED discharge after 2 or fewer doses of intravenous opioids, more than 12 hours elapsed after the first dose of intravenous opioids, low hemoglobin (<5 g/dL), hemodynamic instability, acute stroke, ketamine use in the ED, new SCD drug initiation within 3 months, 3 or more ED visits for acute pain within the prior 7 days, hospital discharge within the prior 7 days, previous enrollment in the current trial, use of a nitric oxide–based drug within 30 days of enrollment, non-English/non-Spanish speaking, pregnancy, or allergy to arginine.[1] Further details are available in the eAppendix in Supplement 3.

Study Procedures

Participants were randomly assigned 1:1 to the intervention or placebo group within 12 hours of receiving their first dose of

Figure. Flow Diagram of Participants in the STArT Trial



STArT indicates Sickle Cell Disease Treatment With Arginine Therapy. Of 2629 patients with sickle cell disease and vaso-occlusive pain screened in a participating emergency department, 741 (28%) were eligible/approached with a guardian present; 293 (40%) consented. Forty-eight (18%) missed at least 1 dose of study drug (26 [20%] in the arginine group and 22 [15%] in the placebo group). Twenty-four (9%) requested the study drug infusion to be slowed from 30 minutes to 60 minutes due to a perceived adverse event (9 [7%] in the arginine group and 15 [11%] in the placebo group). Three patients (1%) had study drug stopped for various concerns, typically associated with a perceived adverse event, by patient request (n = 1) and parental request (n = 2).

[a]Not approached because research staff unavailable (n = 113), parent or guardian unavailable (n = 88), clinician request (n = 2), patient in another study (n = 2), or previously opted out of research/emergency department discharge/other reasons (n = 88).

[b]Not eligible to be randomized because met another exclusion criterion (n = 6), abnormal complete metabolic panel findings (n = 1), found to be ineligible after consent but before randomization (n = 1), or wanted more time/left against medical advice/other reasons (n =11).

ED-based intravenous opioids and after provision of informed consent. Intravenous arginine was chosen over oral supplementation due to our experience of poor adherence to oral formulations among hospitalized children with SCD pain.[11] Intravenous arginine also offers greater bioavailability compared with oral formulations because it bypasses first-pass hepatic metabolism, where orally administered arginine can be significantly degraded by arginase.[7] An initial dose of 200 mg/kg of intravenous arginine was administered to patients randomized to the intervention group, followed by 100-mg/kg doses every 8 hours up to a maximum of 21 doses or until discharge, whichever came first, based on previous studies.[4,18,19] Participants randomized to the placebo group received a small volume of intravenous saline administered at the same rate as intravenous arginine. Participants were followed up daily to capture potential adverse events, daily highest and lowest pain scores experienced, clinical course, laboratory and radiologic assessments, and opioid analgesia use from the time of randomization through day 9 or hospital discharge, whichever came first. Demographic variables, including race and ethnicity, were obtained from the electronic health record. Race and ethnicity were included given known disparities in pain management among individuals with SCD.[20] Chronic pain was defined as patient-reported SCD-related pain on 15 or more days per month for the prior 6 months.[21] ED revisits and hospital readmissions were tracked through 28 days following hospital discharge. The Stoplight Pain Scale[22] was incorporated as a study amendment approved in May 2023, collected once daily by research staff simultaneously with a numeric pain score.

Patient-reported outcomes were obtained within 12 hours of enrollment and at discharge or after 21 doses of study drug administration, whichever came first, through previously described methods.[17,23] A subgroup of patients provided patient-reported outcomes within 7 to 10 days after hospital discharge after a study amendment was approved in May 2023.

Table 1. Baseline Participant Characteristics

Characteristics	Arginine (n = 129)	Placebo (n = 142)
Age, median (IQR), y	14.8 (11.6-18.1)	15.2 (10.7-17.7)
Aged <12 y, No. (%)	36 (27.9)	42 (29.6)
Weight, median (IQR), kg	53.1 (36.7-63.0)	50.9 (35.4-64.2)
Sex at birth, No. (%)		
Female	70 (54.3)	62 (43.7)
Male	59 (45.7)	80 (56.3)
Race, No./total (%)	n = 122	n = 139
American Indian or Alaska Native	2 (1.6)	0
Black or African American	115 (94.3)	134 (96.4)
White	3 (2.5)	5 (3.5)
Multiple (Black or African American and White)	2 (1.6)	0
Hispanic or Latino ethnicity, No./total (%)	13/128 (10.2)	7/142 (4.9)
Genotype: hemoglobin SS and sickle β^0-thalassemia, No. (%)	102 (79.1)	98 (69.0)
Prescribed hydroxyurea, No. (%)	99 (76.7)	107 (75.4)
History of acute chest syndrome, No. (%)	87 (68.0)	107 (76.4)
History of asthma, No. (%)	62 (50.0)	68 (47.9)
Bronchodilator use, No. (%)	78 (62.4)	90 (63.4)
Chronic pain: experienced sickle cell disease pain ≥15 d/mo for last 6 mo, No. (%)	50 (39.4)	60 (42.6)
Health care utilization, No. (%)[a]		
0	46 (35.7)	46 (32.4)
1-2	47 (36.4)	48 (33.8)
≥3	36 (27.9)	48 (33.8)
Hospitalizations in the past 12 mo, No. (%)		
0	27 (20.9)	20 (14.1)
1-2	45 (34.9)	61 (43.0)
≥3	57 (44.2)	61 (43.0)
Duration of current pain crisis, No. (%)	n = 128	
Day of presentation	18 (14.1)	24 (16.9)
1 Day prior to presentation	50 (39.1)	44 (31.0)
2-6 Days prior to presentation	50 (39.1)	47 (33.1)
≥1 Week prior to presentation	10 (7.8)	27 (19.0)
Time from start of intravenous opioids to first study drug infusion, h		
Mean (SD)	8.7 (3.89)	8.6 (4.50)
Median (IQR)	8.3 (5.8-11.6)	7.8 (5.2-11.2)
Intravenous morphine equivalents prior to first study drug infusion, mg/kg		
Mean (SD)	0.5 (0.35)	0.4 (0.20)
Median (IQR)	0.4 (0.3-0.5)	0.4 (0.3-0.5)

[a] Health care utilization is defined as the number of emergency department visits that did not result in hospitalization in the past 12 months.

Outcomes

The primary outcome measure was time to crisis resolution, defined as time from the first study drug delivery to the last dose of parenteral opioids, in hours. Participants were followed up from enrollment to hospital discharge, with electronic medical record review for return visits through 28 days after hospital discharge. Additional outcomes included hospital length of stay, measured as time between the hospital admission order from the ED to time of order placement for hospital discharge; total parenteral opioid use in intravenous morphine equivalents (milligrams per kilogram) from the time of study drug delivery until hospital discharge; change in daily highest, lowest, and Stoplight Pain Scale scores; and change in pain scores and patient-reported outcomes at admission vs discharge and at postdischarge follow-up. Safety outcomes included development of acute chest syndrome, blood transfusions, oxygen use, clinical deterioration, 72-hour and 28-day ED return rates, and rehospitalizations.

Statistical Analyses

After descriptive statistics for covariates and outcomes were assessed by site of enrollment and by study group, asymptotic Van Elteren tests were used to assess the effect of arginine vs placebo on the primary and secondary outcomes, controlling for strata (site and age group). The primary outcome used 2-sided significance testing with an $\alpha = .05$. The secondary outcomes used the Bonferroni-Holm step-down procedure. Patient-Reported Outcomes Measurement Information System (PROMIS) scores for pain interference, pain behavior, and fatigue were compared in a manner similar to the other outcomes, with the exception of stratifying by age groups used to determine survey type (8-17 years or ≥18 years; children aged <8 years were not included in these analyses). A separate analysis was conducted using parent-/caregiver-reported values including patients as young as 5 years old and was not stratified by age. To assess significance of subgroup effects, a linear model for the primary outcome was fit, with the main effect of assigned treatment and the subgroup variable of interest, as well as an interaction between these 2 factors controlling for site and age group. Safety analyses were compared between groups using the Mantel-Haenszel tests, controlling for strata.

To identify patient and site characteristics that may contribute to differences in total parenteral opioid use, we constructed multivariable linear regression models. Prespecified subgroup analyses were conducted by age group (3-11 years vs 12-21 years), use of hydroxyurea, and participant sex. The interaction between assigned treatment and each subgroup factor in a linear model was tested (significance level of $P < .017$). Secondary outcomes were assessed in similar models. Data analysis was performed using SAS version 9.4 (SAS Institute Inc); details are available in the statistical analysis plan in Supplement 2.

Results

Of the 2629 potential participants screened, 274 were randomized and 271 received study drug (129 received arginine and 142 received placebo) (**Figure**). The most common reason for screening failure was development of an exclusion criterion, predominantly ED discharge after achieving sufficient pain relief from parenteral opioids. The enrollment rate

Table 2. Study End Points

Outcomes	Arginine (n = 129)		Placebo (n = 142)		Absolute mean difference (95% CI)	*P* value[a]
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Primary outcome						
Time to crisis resolution, h	81.5 (79.6)	60.8 (34.8 to 109.0)	88.6 (152.2)	65.8 (31.1 to 111.1)	7.2 (−21.6 to 35.9)	.98
Secondary outcomes						
Hospital length of stay, h[b]	102.6 (81.5)	81.9 (49.3 to 134.5)	191.0 (1111.5)	82.6 (45.9 to 135.3)	88.5 (−96.5 to 273.4)	.35
Total parenteral opioids, mg/kg	2.6 (4.5)	1.4 (0.5 to 3.1)	1.9 (2.8)	1.0 (0.4 to 2.3)	0.7 (−0.2 to 1.6)	.33
Change in numeric pain score[c]	4.3 (3.5) [n = 123]	4.0 (1.0 to 7.0)	4.4 (3.2) [n = 137]	4.0 (2.0 to 6.0)	0.03 (−0.79 to 0.85)	.70
Patient-reported outcomes in children aged 8-17 y						
Change in numeric pain score[c]	4.3 (3.4)	4.0 (1.0 to 7.0)	4.2 (3.2)	4.0 (2.0 to 7.0)	0.1 (−0.9 to 1.1)	.95
Change in PROMIS pain interference, T score[c,d]	1.7 (8.9) [n = 109]	1.7 (−1.4 to 6.7)	0.9 (8.0) [n = 105]	1.0 (−3.1 to 4.9)	0.8 (−1.9 to 3.4)	.18
Change in PROMIS pain behavior, T score[c,d]	0.4 (10.5) [n = 108]	0.0 (−1.8 to 3.9)	0.3 (11.2) [n = 106]	0.0 (−2.1 to 3.4)	0.2 (−3.3 to 3.6)	.80
Change in PROMIS fatigue, T score[c,d]	−0.4 (8.9) [n = 109]	0.0 (−4.0 to 3.8)	−0.6 (11.5) [n = 106]	1.0 (−8.0 to 6.1)	0.2 (−3.1 to 3.4)	.44
Patient-reported outcomes in adults						
Change in numeric pain score[c]	4.2 (3.5)	5.0 (1.0 to 7.0)	3.9 (2.4)	4.0 (2.0 to 5.5)	0.3 (−1.2 to 1.8)	.76
Change in PROMIS pain interference, T score[c,d]	1.0 (6.1) [n = 109]	0.0 (−1.7 to 2.9)	0.9 (5.3) [n = 105]	1.9 (−0.9 to 4.2)	0.1 (−3.0 to 3.1)	.57
Change in PROMIS pain behavior, T score[c,d]	1.4 (3.7) [n = 108]	1.1 (−1.3 to 3.2)	1.5 (3.6) [n = 106]	1.5 (0.0 to 3.0)	0.1 (−1.9 to 2.0)	.82
Change in PROMIS fatigue, T score[c,d]	−1.0 (11.2) [n = 109]	0.0 (−8.0 to 3.0)	2.0 (8.0) [n = 106]	1.0 (−1.3 to 5.3)	3.0 (−2.1 to 8.0)	.19

Abbreviation: PROMIS, Patient-Reported Outcomes Measurement Information System.

[a] *P* values for continuous measures are from Van Elteren tests stratified by clinical center and age group.

[b] Length of stay is defined as time from first study drug infusion to discharge.

[c] Change in score is change between emergency department presentation and hospital discharge.

[d] Higher PROMIS scores indicate an increase of the concept/symptom being measured.

surpassed annual targets, but enrollment closed prematurely after reaching 76.1% of the overall target when the second formal interim analysis in June 2024 indicated that conditional power for the primary outcome was less than 6%, even under the original hypothesized effect size of a 17-hour difference in time to crisis resolution. Thus, the data and safety monitoring board recommended stopping the trial for futility. Demographics and patient characteristics were similar between study groups (**Table 1**).

Chronic pain was reported in 41.0% of participants (n = 110), including 34% (n = 26) of children younger than 12 years, 44% (n = 47) of those aged 13 to 17 years, and 51% (n = 32) of adults. Only 50.4% of patients sought emergency care within 24 hours of the start of the current pain episode. Nearly 20% of patients (n = 54) had diagnoses of acute chest syndrome, 18 of which were identified in the ED.

Study drug was delivered to patients a median of 8 hours (IQR, 5.3-11.4 hours) after the first ED dose of intravenous opioid analgesia and a median of 2.2 hours (IQR, 1.6-2.9 hours) after randomization.

Primary Outcome

The median time to crisis resolution was 63.2 hours (IQR, 31.-111.1 hours); 60.1% of participants achieved crisis resolution within 72 hours (eFigure 1 in Supplement 3). Time to crisis resolution strongly correlated with hospital length of stay (r = 0.86; P < .001) (eFigure 2 in Supplement 3). Twenty-three patients experienced crisis resolution within zero hours, with the last dose of intravenous opioid administered prior to study drug delivery (10 in the arginine group and 13 in the placebo group).

There was no significant difference in time to crisis resolution among patients receiving arginine compared with placebo (median, 60.8 hours [IQR, 34.8-109.0 hours] vs 65.8 hours [IQR, 31.1-111.1 hours], respectively; absolute difference, 7.2 hours; 95% CI, −21.6 to 35.9 hours) (**Table 2**). There were also no significant differences identified in time to crisis resolution by predefined subgroups that included sex, age, and hydroxyurea use. Additionally, there were no significant differences based on genotype or the presence of chronic pain.

Although no significant variation in time to crisis resolution by age groups was identified (eFigure 3 in Supplement 3), large variations among individuals and by site were observed (eFigure 4 in Supplement 3). The median and mean times to crisis resolution varied by site by as much as 61 hours and 80 hours, respectively. A post hoc power recalculation to determine the sample size required to identify a 17-hour difference in time to crisis resolution with the observed variation would require more than 900 patients, with more than 450 in each group.

Secondary Outcomes

Total Parenteral Opioids

The mean total parenteral opioids administered to all patients was 2.2 mg/kg (SD, 3.7 mg/kg) of intravenous morphine

Table 3. Serious Adverse Events, Nonserious Adverse Events, and Safety Outcomes by Study Group[a]

	No. (%)	
	Arginine (n = 129)	Placebo (n = 142)
Serious adverse events[b,c]	22 (17.1)	25 (17.6)
Sickle cell anemia with crisis	10 (7.8)	8 (5.6)
Pain	6 (4.7)	9 (6.3)
Acute chest syndrome[d]	2 (1.6)	4 (2.8)
Common clinical nonserious adverse events[c]	81 (62.8)	83 (58.5)
Abdominal pain	10 (7.8)	5 (3.5)
Acute chest syndrome[d]	9 (7.0)	10 (7.0)
Decreased appetite	10 (7.8)	5 (3.5)
Hemoglobin decreased	12 (9.3)	5 (3.5)
Headache	15 (11.6)	14 (9.9)
Hypoxemia[e]	7 (5.4)	11 (7.7)
Nausea	23 (17.8)	23 (16.2)
Pyrexia	18 (14.0)	18 (12.7)
Transfusion	10 (7.8)	9 (6.3)
Vomiting	10 (7.8)	14 (9.9)
Safety outcomes		
Oxygen use	42 (32.6)	42 (29.6)
Return to ED within 28 d	35 (27.1)	46 (32.4)
Blood transfusion	33 (25.6)	30 (21.1)
Acute chest syndrome[d]	29 (22.5)	25 (17.6)
In ED	12 (9.3)	6 (4.2)
After admission	17 (13.2)	19 (13.4)
Return to ED within 72 h	9 (7.0)	8 (5.6)
Clinical deterioration	4 (3.1)	7 (4.9)

Abbreviation: ED, emergency department.

[a] Only participants who were randomized and received an intervention drug (n = 271) were included in this analysis (safety population).

[b] Serious adverse events are defined as any adverse medical occurrence after randomization that results in death, is life-threatening, requires hospitalization or prolongs hospitalization, or causes persistent disability. The majority of serious adverse events involved rehospitalization for pain or prolongation of hospitalization. These data show the total number of patients with at least 1 serious adverse event overall, then by category. There was no difference in serious adverse events between the arginine and placebo groups, with the following additional serious events reported in 1 patient each: acidosis, aspiration, asthenia, drug dependence, gastroenteritis, hallucination, intensive care transfer, intentional overdose, limb discomfort, pyrexia, respiratory distress, and respiratory failure.

[c] Nonserious adverse events with 10 or more patients in either treatment group are shown; all serious adverse events are shown. Serious and nonserious adverse events are mutually exclusive.

[d] Acute chest syndrome was a predefined safety outcome. All cases of acute chest syndrome are included (n = 54), whether identified in the emergency department or after admission. Only 6 cases of acute chest syndrome met the criteria of a serious adverse event, while a total of 19 cases were reported as adverse events.

[e] Hypoxemia was always associated with acute chest syndrome.

equivalents, with a median of 1.2 mg/kg (IQR, 0.4-2.7 mg/kg). No significant differences were identified based on sex, genotype, age, or hydroxyurea use. A history of chronic pain (P = .04) and a duration of current pain of 24 hours or longer (P = .01) were associated with higher total parenteral opioids administered in unadjusted analysis and remained significant in multivariable analysis. No differences were observed between study groups (P = .11). Variations in total parenteral opioid use were observed across sites, with mean and median differences of up to 3.0 mg/kg and 2.2 mg/kg, respectively (eFigure 4 in Supplement 3).

Numeric Pain Scores

Pain scores declined significantly from ED presentation to hospital discharge (median decrease, 4 points [IQR, 2-7 points]; P < .001), with no significant difference between study groups. Additionally, no statistically significant difference in changes among daily highest and lowest reported pain scores were observed between study groups.

Patient-Reported Outcomes

No significant differences in parent- or patient-reported outcomes were noted in participants when comparing presenting patient-reported outcomes with those obtained at discharge (Table 2). However, significant improvements developed by 7 to 10 days after hospital discharge (eTable 2 in Supplement 3) that did not significantly differ based on study group. A sensitivity analysis found that only very implausible missingness patterns would result in any change in the conclusions.

Safety

There were no differences in prespecified safety outcomes between study groups. The rates of adverse events and serious adverse events were also similar, there were no unexpected study drug-related adverse events (**Table 3**), and there were no deaths. Overall, there were no statistically significant differences in study outcomes for the per-protocol efficacy population that included all participants in the intention-to-treat population who received 90% or more of the required study drug doses (eTable 3 in Supplement 3).

Discussion

In this phase 3 RCT of arginine therapy for children and young adults with SCD hospitalized for acute pain, time to crisis resolution was not significantly different between the intravenous arginine and placebo groups. To date, all US-based phase 3 RCTs targeting SCD acute pain have failed to demonstrate an effect on shortening hospital length of stay or time to crisis resolution after promising results from phase 2 trials.[4,11,12,14,15,24-30] The current trial is the latest addition to this list, stopped early for futility to achieve its primary end point.[31]

As one of the largest pediatric SCD acute pain RCTs to date, this study underscores the challenges clinical trials face due to shorter hospital stays and wide interpatient and site variability. Time to crisis resolution was chosen as this trial's primary end point as it remains the favored FDA outcome for regulatory approval of new drugs for treatment of acute pain in SCD. Data from this trial and others confirm that time to crisis resolution strongly correlates with length of stay.[4,31] However, time to crisis resolution is a subjective outcome that may vary by institution, age, or certain patient populations, regardless of treatments administered.[4,31,32] Analysis of the placebo group

of the current trial identified key patient- and site-level factors present at the time of trial enrollment that were independently associated with longer time to crisis resolution and greater total parenteral opioid use.[31] In contrast with past single-center studies that have observed age-based differences in this outcome,[4,32] the current study did not, likely due to its being a multicenter trial with wide variability in site-based practices.[31]

Both time to crisis resolution and length of stay may be less than ideal clinical end points for SCD acute pain trials given trends across the US toward shorter hospital length of stay over the last 25 years.[4,11,31,32] The median length of stay in the MAGiC study,[24] a phase 3 RCT of intravenous magnesium to treat children with SCD acute pain episodes that enrolled patients from 2010 to 2013, was less than 56 hours. Although the MAGiC study failed to detect a difference between study groups, it was the first phase 3 RCT treating SCD acute pain episodes to achieve its enrollment milestones.[33] Prior to the involvement of the PECARN, which fostered strong collaboration between academic hematologists and pediatric emergency medicine physicians, acute SCD pain trials were failing due to poor enrollment,[34] which prohibited a critical analysis of clinical trial end points until recently.[31]

Most of the current trial's participants achieved crisis resolution within the first 2 to 3 days after admission, and the total parenteral opioids administered in the current trial (mean, 2.2 mg/kg, and median, 1.2 mg/kg) were less than half the dose delivered more than 20 years ago in a study in which arginine therapy significantly decreased intravenous opioid use by more than 50%.[11] Thus, it may not be possible to detect a difference in time to crisis resolution or total opioid use in US trials regardless of the intervention. At international sites, length of stay often approaches a week or longer, which may explain the positive findings of several arginine phase 2 trials in Nigeria and Egypt, where statistically significant reductions in time to crisis resolution of greater than 24 hours were noted.[12,13,15]

This study's findings aligned with previous RCTs in that patient-reported outcomes, an end point that is also of interest for FDA regulatory approval,[35] did not improve by hospital discharge in either study group despite significant improvement in numeric pain scores.[4] However, statistically significant and clinically meaningful improvements occurred 7 to 10 days after hospital discharge that were similar in both study groups. To date, no SCD acute pain trials have identified changes in patient-reported outcomes from hospital admission to discharge that validates their use[4,24]; overlap in 7-day recall at discharge likely confounds results when patient length of stay is often less than 3 days.

No safety concerns were noted, adding to numerous national and international studies demonstrating arginine safety.[4,11,13-16,36]

Limitations

This study has several limitations. First, larger-than-expected outliers and standard deviations, additional confounders, a frequently short length of stay, and site-based practice variations identified in the current trial decreased precision,[31] likely rendering the trial underpowered to detect differences in outcomes that might have been identified with a larger cohort. However, a sample size of 900 patients is not feasible for this rare disease in the US. Second, pain scores recorded were obtained at different times of day and may have been influenced by recent treatments with analgesics that were not adjusted for; future trials should consider standardizing the timing of daily pain score assessments. Third, pain scale assessment and postdischarge follow-up patient-reported outcomes were available only for a subset of patients, limiting power to identify potential differences. Fourth, other subgroup comparisons were also likely underpowered. Fifth, pain mechanisms are multifactorial, and not all pain is vaso-occlusive. It is unlikely that a single therapy can ameliorate all SCD acute pain. For example, a surprising 41% of participants reported chronic pain, including a third of patients younger than 12 years. Pain trajectories and response to therapies may be different among patients with chronic pain, which could adversely impact the ability to detect differences in pain-related end points. Currently, no drug has received FDA regulatory approval for shortening SCD acute pain episode duration, highlighting the complexity of pain pathophysiology.[37,38] Initiation of novel SCD pain therapeutics at home at the first sign of acute pain to decrease ED visits may be a better strategy for future clinical trials.

Conclusions

Among children and young adults presenting to the ED with SCD acute pain episodes, arginine therapy did not shorten time to crisis resolution compared with placebo. Emerging evidence suggests that new SCD acute pain trials are also likely to yield null or inconclusive results if they continue relying on traditional designs that focus on this same outcome measure. To advance the field, novel clinical trial approaches are needed, as well as coordinated stakeholder efforts to identify new end points or surrogate biomarkers that can more accurately capture meaningful clinical benefit.

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