RESEARCH LETTER

blood advances

TO THE EDITOR:

Patient-reported outcomes in children with sickle cell disease at presentation for an acute pain episode

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Patient reported outcomes (PROs) provide multidimensional perspectives on the impact of pain[1-5] and have been assessed using the Patient Reported Outcomes Measurement Information System (PROMIS) in children with sickle cell disease (SCD) during outpatient visits,[3,4] acute care utilization for pain,[4,6] and in clinical trials to measure the effect of interventions.[7-9] Here, we report the feasibility of collection of PROs of pain interference and fatigue at enrollment (baseline) from participants 3 to 21 years of age enrolled in a phase 2 randomized double-blind placebo-controlled trial of intravenous arginine therapy for acute SCD pain (NCT02536170),[10] and examine the impact of an acute pain episode on these PROs.

Study design has been previously published.[10] At, or soon after enrollment, study participants and/or their parents completed the self-report pediatric or parent-proxy version of the 8-item PROMIS Pediatric Pain Interference v1.0 Short Form (SF) 8a and the 10-item PROMIS Pediatric Fatigue v1.0 SF 10a,[2-4,6] which generated domain-specific standard T-scores.[11] These questionnaires have a 7-day recall and are valid, reliable, and responsive to change in pain in SCD.[2-4,6] Demographic, clinical, and laboratory data were as collected during the clinical trial, and prior health care utilization (HCU) for pain represented the sum of emergency department visits and hospitalizations for pain in the 12-month period before enrollment. We defined high HCU for pain as ≥3 episodes of HCU for pain, given that this threshold is a marker of severity in SCD.[12,13] This study was approved by the Institutional Review Board at Emory University and was conducted in accordance with the Declaration of Helsinki.

Ninety-eight (mean age, 12.8; standard deviation [SD], 3.7 years; 53.1% female) of the 108 enrolled participants (90.7%) had at least 1 completed PRO (n = 94, for pain interference; n = 98, for fatigue), either by child self-report or by parent-proxy report (for n = 4, we retained self-report versions because both self-report and parent-proxy forms were completed). Both pain interference and fatigue domains were completed for 94 participants (87%), and neither of the domains for 10 participants (9.3%). For 64 participants (mean age, 14.1; SD, 3 years), at least 1 self-report pediatric PROMIS questionnaire was available, and for 35 participants, at least 1 parent-proxy PROMIS questionnaire was available (mean age, 10.5; SD, 3.6 years). Our experience confirms that collection of pain-related PROs is feasible in a clinical trial of an acute pain intervention in SCD, consistent with previous experience in observational and intervention studies of acute pain[4,6,14,15] in SCD.

Participant characteristics are reported in Table 1. Domain scores are reported in Table 2 and supplemental Figure 1. To determine the severity of patient reported symptoms, we used thresholds for self-report pediatric pain interference in SCD, in which a T-score of ≤48 represents mild symptoms, 49 to 64 represents moderate symptoms, and >64 represents severe symptoms.[1] Because severity thresholds are not described for self-report pediatric fatigue in SCD, we used thresholds established in

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The full-text version of this article contains a data supplement.

Table 1. Demographic and clinical characteristics for all enrolled participants and participants included in the analyses

	All	Included
	n = 108	n = 98
Age, mean (SD)	12.6 (3.8)	12.8 (3.7)
Sex, n (%)		
Male	52 (48.1)	46 (46.9)
Female	56 (51.9)	52 (53.1)
Genotype, n (%)		
HbSS/HbSβ^0 thalassemia/HbS-OArab	78 (72.2)	72 (73.5)
HbSC/HbSβ$^+$ thalassemia	30 (27.8)	26 (26.5)
Hydroxyurea use, n (%)		
No	35 (32.4)	31 (31.6)
Yes	73 (67.6)	67 (68.4)
HCU in prior year*, median (IQR)	3 (2,6)	3 (2,6)
HCU for pain in prior year*, median (IQR)	2 (1,4.5)	2 (1,4)
Proportion with ≥3 episodes of HCU for pain in prior year*, n (%)	51 (47.7)	45 (46.4)
Highest pain score at presentation, median (IQR)	9.00 (8,10)	9.00 (8,10)
Prescribed medications, n (%)		
Oral opioids (hydrocodone, oxycodone, hydromorphone, morphine, or tramadol)†	105 (97.2)	95 (96.9)
Nonsteroidal Anti-inflammatory (ibuprofen, naproxen or meloxicam)	101 (93.5)	93 (94.9)
Adjunctive analgesics including muscle relaxants (clonidine, gabapentin, amitriptyline, lidocaine, cyclobenzaprine, or methocarbamol)	30 (27.8)	24 (24.5)
Methadone	1 (0.9)	1 (1)
Laboratory values at enrollment, mean (SD)		
WBC (X 10-9/L)	12.3 (5.1)	12.3 (5.1)
Hemoglobin (g/dL)	9.3 (1.7)	9.3 (1.7)
Mean corpuscular volume (fL)	86.8 (12.6)	86.9 (12.5)
Platelets (X 10-9/L)	367.9 (166.7)	363.9 (163.4)

No statistically significant differences between included participants (at least one PROMIS score, n = 98) and excluded (no PROMIS score, n = 10), except for excluded participants having a higher proportion of prescription of adjunctive analgesics ($P = .026$).

Among those included, those prescribed hydroxyurea were more likely to have HbSS/HbSβ^0 thalassemia/HbS-OArab genotype ($P < .001$), lower hemoglobin ($P < .001$), higher mean corpuscular volume ($P < .001$), higher platelet count ($P = .039$), and higher HCU for pain in the prior year ($P = .031$).

IQR, interquartile range; WBC, white blood cells.

*n=107 (entire cohort) and 97 (included) respectively.

†Includes combination medications.

juvenile idiopathic arthritis and systemic lupus erythematosus,[16] in which a T-score of ≥57.5 represents moderate fatigue, and ≥67.5 represents severe fatigue. Most self-report pediatric pain interference scores (n = 53, 88.3%) met the threshold for moderate (n = 26) or severe (n = 27) pain interference, and most self-report pediatric fatigue scores (n = 41, 64%) met the threshold for moderate (n = 25) or severe (n = 16) fatigue. Our findings indicate that the majority experience at least moderate pain interference and fatigue when they experience pain that results in an acute care visit that requires parenteral opioids. As compared to those with mild pain interference, those with moderate to severe pain interference were more likely to have been prescribed NSAIDs ($P = .034$). We found that females were more likely to have moderate to severe fatigue compared with males (78.1% females vs 50% males; $P = .037$), consistent with published reports of higher fatigue in female children[3] and adults with SCD.[17,18] We also found that those that were prescribed hydroxyurea (HU) were more likely to have at least moderate fatigue than those that were not (73.3% vs 42.1%; $P = .036$). However, the prescription of HU was associated with both a severe sickle cell genotype and high HCU for pain, so the relationship between fatigue and HU may be confounded by disease severity or may reflect the prescription of HU to those with more severe disease, as has been previously reported.[19] No other differences in demographic, clinical, or laboratory characteristics between those who had at least moderate symptoms as compared with those who had mild symptoms were observed, including lack of differences in hemoglobin levels or mean corpuscular volume.

We then examined the effects of age (<12 years and ≥12 years), sex, HU, and history of high HCU for pain (independent variables) on PROs (dependent variables) in bivariable and multivariable models using general linear regression (Table 2). We found no differences in fatigue and pain interference by age in this study, different from reports of higher pain interference during routine clinic visits in children >12 years compared with younger children.[3] In bivariable models, we observed a moderate effect size (ES, 0.45; $P = .070$) for female sex on self-reported fatigue. In multivariable models adjusted for all clinical covariates, we observed moderate effect sizes for female sex on self-report fatigue (ES, 0.48; $P = .072$) and pain interference (ES, 0.47; $P = .095$) scores, but these were not statistically significant. Higher pain interference and fatigue have been reported in female children and adults with SCD,[3,17,18] so the lack of significant associations during an acute pain episode must be examined in future studies.

We did not observe an association between genotype and PROs, consistent with reports from outpatient visits.[3] We also did not observe an association of PROs with high HCU for pain, different from reports in which pain interference and fatigue are correlated with HCU for pain.[20] We did not find an association between HU and pain interference, consistent with lack of significant effects of HU on change in pain interference and other pain-related PROs after an acute pain episode.[6] Contrary to findings in children with chronic pain conditions including SCD during outpatient visits,[21] we did not observe a significant correlation between pain interference or fatigue with the highest pain score reported at baseline (all Pearson product moment correlations, $-0.2 < \rho < 0.2$; $P > .1$). Similarly, we did not observe significant correlations between pain interference or fatigue with hemoglobin or mean corpuscular volume values, contrary to reported associations[18,22] in SCD during clinic and hospital visits.

The lack of association between PROs and clinical correlates in this study may have several possible explanations: effects may be minimized during an acute pain episode, may not have been observed after accounting for the effect of other clinical covariates, or have lacked adequate power to detect an association. The presence of chronic pain was not collected in this study. Because chronic pain impacts PROs,[17] it is crucial to study the impact of acute pain on PROs among those with chronic pain, as is being done in a subsequent randomized study of arginine in SCD (NCT04839354).[23]

Table 2. Least squares (LS) mean differences with 95% Wald confidence intervals, *P* values, and effect sizes† of pain interference and fatigue outcomes. Both unadjusted models and models adjusted for clinical covariates are shown

	Pain interference				Fatigue			
LS-means (95% CI)	Self-report n = 60	P (ES)	Parent-proxy n = 34	P (ES)	Self-report n = 64	P (ES)	Parent-proxy n = 34	P (ES)
Overall	60.6 (58.1,63.1)	–	63.6 (60.2,67.1)	–	59.4 (56.2,62.5)	–	58.6 (54.1,63.1)	–
Unadjusted								
Age, y								
<12	58.1 (52.3,63.9)	0.297 (0.35)	63.5 (58.7,68.4)	0.896 (0.04)	55.3 (47.5,63.1)	0.204 (0.43)	57.2 (51.3,63.0)	0.317 (0.34)
≥12	61.5 (58.8,64.2)		63.9 (60.4,67.4)		60.7 (57.5,63.9)		61.5 (55.0,68.1)	
Sex								
Male	58.6 (55.2,62.0)	0.116 (0.41)	64.7 (60.8,68.6)	0.576 (0.18)	56.5 (52.1,60.9)	0.070 (0.45)	57.9 (50.9,64.8)	0.785 (0.10)
Female	62.6 (59.0,66.1)		62.9 (57.7,68.1)		62.2 (57.9,66.5)		59.1 (53.1,65.1)	
Genotype								
HbSS/HbSβ^{0}thalassemia /HbS-OArab	60.5 (57.9,63.2)	0.935 (0.03)	64.0 (59.6,68.3)	0.791 (0.10)	59.8 (56.6,62.9)	0.704 (0.14)	59.9 (54.1,65.7)	0.355 (0.32)
HbSC/HbS-β$^+$thalassemia	60.8 (54.4,67.2)		63.0 (57.1,68.9)		58.0 (49.3,66.7)		55.8 (49.1,62.6)	
Hydroxyurea use								
No	60.5 (54.9,66.2)	0.981 (0.01)	64.0 (58.1,69.9)	0.881 (0.06)	57.3 (49.9,64.8)	0.479 (0.23)	55.1 (48.0,62.2)	0.234 (0.42)
Yes	60.6 (57.9,63.3)		63.5 (59.1,67.8)		60.2 (57.0,63.4)		60.5 (54.8,66.2)	
HCU for pain in past year								
<3 visits	59.8 (56.6,63.1)	0.276 (0.29)	64.1 (60.2,68.1)	0.789 (0.09)	58.3 (54.1,62.6)	0.393 (0.22)	56.6 (51.3,62.0)	0.399 (0.29)
≥3 visits	62.5 (58.9,66.1)		63.2 (57.7,68.8)		61.1 (56.3,65.9)		60.3 (53.3,67.4)	
Adjusted*								
Age, y								
<12	59.6 (53.2,66.0)	0.437 (0.28)	63.5 (58.1,68.9)	0.969 (0.01)	55.2 (46.5,63.8)	0.219 (0.44)	57.0 (50.4,63.6)	0.758 (0.12)
≥12	62.2 (59.3,65.2)		63.3 (58.4,68.3)		60.7 (57.0,64.4)		58.5 (50.9,66.1)	
Sex								
Male	58.5 (54.7,62.2)	0.095 (0.47)	64.4 (59.5,69.3)	0.684 (0.15)	55.9 (50.8,61.0)	0.072 (0.48)	57.0 (48.8,65.2)	0.890 (0.05)
Female	62.8 (58.8,66.8)		62.9 (57.2,68.6)		62.0 (57.1,66.9)		57.7 (51.5,63.9)	
Genotype								
HbSS/HbSβ^{0}thalassemia /HbS-OArab	62.0 (57.8,66.1)	0.712 (0.18)	64.8 (58.7,70.9)	0.680 (0.21)	60.2 (55.1,65.3)	0.698 (0.18)	56.7 (48.9,64.5)	0.766 (0.13)
HbSC/HbS-β$^+$ thalassemia	60.3 (53.4,67.2)		62.7 (55.7,69.7)		58.0 (49.1,66.9)		58.4 (51.6,65.3)	
Hydroxyurea use								
No	62.1 (56.1,68.2)	0.622 (0.23)	64.8 (57.6,72.0)	0.692 (0.22)	59.1 (51.2,67.0)	0.999 (0.00)	54.2 (45.3,63.1)	0.352 (0.50)
Yes	60.0 (55.1,64.9)		62.7 (56.2,69.2)		59.1 (52.8,65.3)		60.6 (52.3,69.0)	
HCU for pain in past year								
<3 visits	58.9 (55.1,62.7)	0.146 (0.40)	64.3 (59.9,68.8)	0.904 (0.05)	57.4 (52.6,62.1)	0.387 (0.23)	55.5 (49.5,61.4)	0.329 (0.37)
≥3 visits	62.6 (58.8,66.4)		63.9 (57.6,70.2)		60.3 (55.1,65.5)		60.2 (52.3,68.1)	

*Multivariable models consider the primary exposure and adjust for all other covariates; age was treated continuously when not considered the primary exposure.
†ES = Effect size, interpreted as small (0.2), moderate (0.5), and large (0.8) and calculated by dividing outcome least squares mean differences by respective pooled standard deviations from the study sample.

In summary, we report that PROs complement clinical outcomes and assessment of the impact of acute pain in SCD, concordant with the recommendations from the American Society of Hematology to include PROs as endpoints in clinical trials.[24] This study also indicates the need to examine the effects of clinical and biological correlates on PROs in adequately powered studies, specifically in the context of an acute painful episode.

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