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Sex and frequency of pain episodes are associated with acute pain trajectories in adolescents with sickle cell disease

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Abstract

Introduction/Objective: Acute pain episodes are a major cause of health care utilization (HCU) in sickle cell disease (SCD), and adolescence is associated with increased pain frequency. We sought to determine whether there were differences in acute pain trajectories by sex and frequency of pain episodes among adolescents with SCD who presented to the emergency department (ED).

Methods: Retrospective review of electronic health records from a large, multicampus, pediatric SCD program.

Results: Of the 113 adolescents included, the mean age was 16.6 (SD 0.9), 41.6% (n = 47) were female, 77.9% (n = 88) had HbSS or a similarly severe genotype, and 43.4% (n = 49) had ≥3 episodes of HCU for pain, which we defined as having history of high HCU for pain. Those with a history of high HCU for pain had higher mean pain intensity scores at presentation, were more likely to receive either intravenous or intranasal opioids, and were more likely to be hospitalized. In a model considering the 3-way interaction between sex, history of high HCU for pain, and follow-up time from the initial pain intensity score, adjusted for opioid per kilogram body weight, and prescription of hydroxyurea, adolescent female patients with high HCU for pain had the slowest decline in pain intensity during treatment for acute pain in the ED.

Conclusion: Sex and history of high HCU for pain are associated with acute pain trajectories in adolescents with SCD presenting to the ED. These novel findings should be confirmed in future prospective studies.

Keywords: Sickle cell, Pain, Vaso-occlusive crisis, Pain episode, Sex, Trajectories

1. Introduction

Pain is the most common complication of sickle cell disease (SCD) and is associated with significant morbidity,[14] poor health-related quality of life,[19] and premature mortality.[7,24] Acute pain episodes are the major cause of adult and pediatric SCD emergency department (ED) visits[15] and hospitalizations. Adolescence is associated with an increasing frequency of complications in SCD, particularly pain.[13] Children aged 15 to 18 years with SCD make up the largest group of children admitted for pain,[12] and approximately 40% of children aged 16 to 18 years have at least 1 episode of health care utilization for pain over a 1-year period.[13] The period around adolescence is associated with sex differences in pain[21,22] in other painful conditions, but sex differences in acute pain during adolescence are not well described in SCD. In addition, a subgroup of adolescents has high health care utilization (HCU) for pain,[13] but it is not known whether their acute pain experience and trajectories differ from those who do not have frequent HCU for pain.

In this study, we sought to determine whether there were differences in acute pain trajectories by sex and frequency of pain episodes among adolescents with SCD who presented to the ED. Given the higher pain burden experienced by adolescents aged

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15 to 18 years compared with their younger counterparts, we focused our study on adolescents in this age group.

2. Methods

This was a retrospective study completed at a large, urban, multicampus, academic pediatric SCD program in the United States using existing electronic health record (EHR) data. This study was approved by the Institutional Review Board at the Children's Healthcare of Atlanta.

2.1. Inclusion criteria

All adolescents of 15 to 18 years of age with SCD who previously had either an outpatient or inpatient encounter at least once in the prior 2 years and who had a subsequent ED visit for SCD-related pain in 2019 were identified. *A priori*, we selected the last ED visit for SCD-related pain in 2019 for each patient as the index ED visit under study, regardless of pain severity or type of treatment received. In identifying the last ED visit in 2019, if there were back-to back ED visits for pain, defined as ED visits for SCD pain that occurred within 7 days of each other, we considered the multiple ED visits to be part of the same pain episode and used the initial ED visit of the series of visits as the index ED visit under study.

2.2. Exclusion criteria

Patients with SCD with a co-occurring pain condition where pain exacerbations could be similar to SCD pain were excluded. We excluded ED visits at which (1) ≤1 pain intensity score was recorded during the visit, (2) adolescents received analgesia in the ED or en route to ED through emergency medical services before documentation of the first pain intensity score, (3) adolescent was transferred from or to another facility before or after presentation at our center, or (4) for visits where pain was explained by an alternative diagnoses or according to study investigators was unlikely to be an SCD-related acute pain episode.

2.3. Demographic and clinical characteristics

Demographic and clinical data were abstracted from the EHR. We calculated past health care utilization (HCU) for pain as the sum of all ED visits and hospitalizations for pain in the 12 months prior to the index ED visit under study. We defined a patient as having high HCU if they had ≥3 visits in the 12 months for pain prior to the index ED visit. The threshold of ≥3 visits in the 12 months for pain is frequently used as a marker of severity in SCD.[23,27] Medication history was obtained by review of both outpatient prescriptions and clinical notes. Medications of interest included opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and adjunctive analgesics for pain. A past diagnosis of avascular necrosis (AVN) was determined based on the review of radiology reports. To calculate steady-state hemoglobin values, we took an average of 2 outpatient steady-state hemoglobin values (if available) in the past year. Pain-related variables collected in the context of clinical care, including pain intensity and the number of locations of reported pain, and medications (opioids, NSAIDs) received were abstracted from the medical record for ED visit under study. We calculated time to receiving time to receiving opioid analgesia referent to the time of arrival to the ED. Length of stay (LOS) was calculated amongst those discharged home as the time between arrival and discharge from the ED. We calculated longitudinal trajectories of pain intensity scores referent to the time of assessment and value of the initial pain intensity score in the ED up to the time of assessment and value of the final pain intensity score in the ED prior to discharge home or admission to the inpatient floor. This period was designated as the "follow-up time" period. We analyzed up to the first 360 minutes (6 hours) from the initial pain score because this represented approximately the 96th percentile (354 minutes) of length of time from the first pain score for the entire cohort. We also counted the number of pain assessments available per individual. Opioids from all routes (intranasal, intravenous, or oral) administered up to the assessment of the final pain score before 360 minutes or up to 360 minutes (to correspond with trajectories of pain intensity) were converted to oral morphine milligram equivalents (MME) as per standard conversion ratios[1,18] (1 mg intravenous [IV] morphine = 3 MME, 1 mg IV hydromorphone = 20 MME, 1 μg intranasal [IN] fentanyl = 0.16 MME, 1 μg IV fentanyl = 0.3 MME, 1 mg IV nalbuphine = 3 MME, 1 mg oral hydrocodone = 1 MME, 1 mg oral oxycodone = 1.5 MME), and thereafter, MME was calculated per kilogram of body weight (MME [kg]).

2.4. Statistical analysis

All statistical analyses were performed in CRAN v.4.0.2 (Vienna, Austria) and SAS v.9.4 (Cary, NC). We used descriptive statistics to describe clinical, demographic, and pain-related variables of interest overall, by sex and by history of high HCU for pain. Differences were tested for statistical significance using 2-sample *t*-tests and χ^2 tests of independence or their nonparametric equivalents (ie, Wilcoxon rank–sum, Kolmogorov–Smirnov, and Fisher exact tests). To study pain trajectories over time, we used general linear mixed models through the PROC MIXED procedure in SAS. We first examined a bivariable model, considering the relationship between follow-up time and pain score for the entire cohort. Subsequently, we considered main effects for sex, history of high HCU for pain, and the combination of sex with high HCU for pain. Each of these main effects were statistically interacted with follow-up time, with significant slopes indicating differences in pain score trajectories. All relationships were considered unadjusted for confounders, adjusted alone for MME (in kilograms), and adjusted both for MME (in kilograms) and prescription of hydroxyurea in the last 12 months. For all general linear mixed models, follow-up time, patient sex, HCU, and their various interactions were treated as fixed effects; concurrently, participant-level intercepts and slopes for follow-up time were treated as random effects (ie, random intercepts and random slopes), to account for heterogeneity in pain scores, as well as heterogeneity in change over time between individuals. Time was modeled as a linear term, and degrees of freedom were estimated using the Kenward–Roger method. An unstructured covariance matrix was used in all regression models and calculated separately for main effects when possible. Results from mixed models are presented as β estimates (ie, slope) with 95% confidence intervals.

3. Results

One hundred thirteen patients had ED visits that met study inclusion criteria.

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics of the 113 patients included are presented in **Table 1** for the entire cohort, as well as by sex and history of high HCU for pain. The mean age was 16.6 (SD: 0.9) years, and 41.6% were female. The mean body mass index (BMI) was higher among female patients ($P = 0.006$) and those with high HCU ($P = 0.004$). The majority (n = 88, 77.9%)

Table 1

Demographic and clinical characteristics.

Characteristic	Overall	Sex			HCU		*P*
		Male	Female	*P*	Low HCU	High HCU	
n	113	66	47		64	49	
Age (mean [SD])	16.6 (0.9)	16.7 (0.9)	16.6 (0.9)	0.466	16.5 (0.9)	16.8 (0.8)	0.170
Sex (n, %)							
Male	66 (58.4)				40 (62.5)	26 (53.1)	0.414
Female	47 (41.6)				24 (37.5)	23 (46.9)	
Weight in kilograms (mean [SD])	62.9 (16.5)	61.8 (15.4)	64.4 (18)	0.412	59.7 (14)	67 (18.6)	**0.018**
Body mass index (mean [SD])*	22.3 (5.3)	21.1 (4.1)	24 (6.4)	**0.006**	21 (3.9)	23.9 (6.4)	**0.004**
Genotype (n, %)							
Hemoglobin SS/Hemoglobin S-β^0 thalassemia/Hemoglobin S-OArab	88 (77.9)	49 (74.2)	39 (83.0)	0.383	46 (71.9)	42 (85.7)	0.127
Hemoglobin SC/Hemoglobin S-β+ thalassemia	25 (22.1)	17 (25.8)	8 (17.0)		18 (28.1)	7 (14.3)	
Presence of avascular necrosis (n, %)	17 (15.0)	10 (15.2)	7 (14.9)	1	7 (10.9)	10 (20.4)	0.258
HCU for pain in past 12 mo (median [IQR])	2 [1, 5]	1[0, 4.8]	2 [1, 5.5]	0.152	1 [0, 1]	6 [4, 9]	**<0.001**
Presence of 3 or more visits in the part 12 mo (n, %)	49 (43.4)	26 (39.4)	23 (48.9)	0.414			
Disease-modifying therapy (hydroxyurea or L-glutamine) in past 12 mo (n, %)	73 (64.6)	42 (63.6)	31 (66)	0.956	33 (51.6)	40 (81.6)	**0.002**
Hydroxyurea	72 (63.7)	41 (62.1)	31 (66.0)	0.826	32 (50.0)	40 (81.6)	**0.001**
L-Glutamine	11 (9.7)	4 (6.1)	7 (14.9)	0.196	2 (3.1)	9 (18.4)	**0.009**
Chronic transfusion therapy in past 3 mo	5 (4.4)	4 (6.1)	1 (2.1)	0.399	4 (6.2)	1 (2.0)	0.386
Home medications (n, %)							
Short-acting opioids (hydrocodone, oxycodone, hydromorphone, tramadol, or oral morphine-immediate release)	109 (96.5)	63 (95.5)	46 (97.9)	0.639	60 (93.8)	49 (100.0)	0.131
Long-acting opioids (methadone or oral morphine-controlled release)	5 (4.4)	2 (3.0)	3 (6.4)	0.647	0 (0.0)	5 (10.2)	**0.013**
NSAID							
Ibuprofen/naproxen	100 (88.5)	60 (90.9)	40 (85.1)	0.513	56 (87.5)	44 (89.8)	0.935
Celecoxib/meloxicam	9 (8.0)	4 (6.1)	5 (10.6)	0.486	0 (0.0)	9 (18.4)	**<0.001**
Adjunctive pain medications	39 (34.5)	21 (31.8)	18 (38.3)	0.608	12 (18.8)	27 (55.1)	**<0.001**
Clonidine	9 (8.0)	5 (7.6)	4 (8.5)	1	1 (1.6)	8 (16.3)	**0.009**
Gabapentin/pregabalin	9 (8.0)	3 (4.5)	6 (12.8)	0.16	0 (0.0)	9 (18.4)	**<0.001**
Amitriptyline	1 (0.9)	1 (1.5)	0 (0.0)	1	0 (0.0)	1 (2.0)	0.433
Muscle relaxants (methocarbamol, cyclobenzaprine, or tizanidine)	37 (32.7)	21 (31.8)	16 (34.0)	0.964	12 (18.8)	25 (51.0)	**0.001**
Baseline hemoglobin g/dL (mean [SD])†	9.8 (1.6)	10 (1.8)	9.5 (1.4)	0.153	9.7 (1.8)	9.8 (1.4)	0.78

Hypothesis testing done by *t* test with equal variances or non-parametric equivalent (ie, Wilcoxon rank sum test) for continuous variables and χ^2 with Yates continuity correction/Fisher exact test for categorical variables.
* n = 110.
† n = 105.
HCU, health care utilization; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drugs.

had HbSS or a similarly severe genotype (HbSβ^0 thalassemia and Hemoglobin SO-Arab), and there were no differences by sex or history of high HCU for pain. The median number of episodes of HCU for pain in 12 months was 2 (interquartile range [IQR] 1–5). Of the total, 43.4% (n = 49) patients had ≥3 episodes of HCU for pain in the 12 months prior to the index ED visit, and there were no sex differences in the history of high HCU for pain. Patients with known AVN comprised 15% (n = 17) of the total cohort with no differences in the history of known AVN between sexes or with history of high HCU for pain.

Most patients (64.6%, n = 73) were prescribed disease-modifying therapies for SCD, but patients with high HCU were more likely to be prescribed hydroxyurea ($P = 0.001$) or L-glutamine ($P = 0.009$). On review of prescribed medications at home, almost all patients were prescribed short-acting opioids and NSAIDs, but those with high-HCU for pain were more likely to receive celecoxib or meloxicam ($P < 0.001$). A minority (n = 5, 4.4%) were prescribed long-acting opioids or methadone, but all of these individuals had high HCU for pain ($P = 0.013$). Approximately one-third (n = 39, 34.5%) were prescribed adjunctive medications for pain, which were more likely to be prescribed in those with high HCU for pain ($P < 0.001$).

3.2. Outcomes in emergency department

Characteristics of the index ED visit under study are presented in **Table 2** for the entire cohort, as well as by sex and history of high HCU. Most participants (n = 86, 76.1%) had taken either an opioid or an NSAID before presentation to the ED. There was no difference in mean initial pain intensity scores at presentation by sex, but mean pain intensity score was slightly higher in those with high HCU for pain. The mean number of pain locations was approximately 2 (SD 1), and there were no differences between the sexes or by history of high HCU for pain. The mean time to

Table 2

Pain and analgesia received in the emergency department (ED).

Characteristic	Overall	Sex			HCU		*P*
		Male	Female	*P*	Low HCU	High HCU	
n	113	66	47		64	49	
Opioid use prior to ED visit (n, %)	57 (50.4)	37 (56.1)	20 (42.6)	0.221	35 (54.7)	22 (44.9)	0.400
NSAID use prior to ED visit (n, %)	59 (52.2)	32 (48.5)	27 (57.4)	0.454	31 (48.4)	28 (57.1)	0.467
Opioid or NSAID use prior to ED visit (n, %)	86 (76.1)	51 (77.3)	35 (74.5)	0.904	46 (71.9)	40 (81.6)	0.326
Initial pain score (mean [SD])	7.8 (2)	7.6 (2.2)	8.1 (1.7)	0.207	7.4 (2.2)	8.3 (1.6)	**0.023**
No. of pain locations (mean [SD])	1.9 (1)	2 (1.1)	1.8 (1)	0.234	1.9 (1)	1.9 (1.1)	0.887
Time to opioid analgesia in minutes (mean [SD])*	36.2 (25.5)	33.1 (18.6)	40.8 (32.8)	0.119	33.4 (22.3)	39.8 (29)	0.188
Medications received in ED (n, %)							
Intravenous opioid (morphine, hydromorphone, nalbuphine, or fentanyl)	93 (82.3)	53 (80.3)	40 (85.1)	0.682	45 (70.3)	48 (98.0)	**<0.001**
Intranasal fentanyl	65 (57.5)	42 (63.6)	23 (48.9)	0.172	38 (59.4)	27 (55.1)	0.792
Intravenous opioid or intranasal fentanyl	106 (93.8)	63 (95.5)	43 (91.5)	0.447	57 (89.1)	49 (100.0)	**0.018**
Intravenous ketorolac	91 (80.5)	52 (78.8)	39 (83.0)	0.754	51 (79.7)	40 (81.6)	0.985
Intravenous opioid or intranasal fentanyl or intravenous ketorolac	113 (100)	66 (100.0)	47 (100.0)	NA	64 (100.0)	49 (100.0)	NA
Oral opioid (hydrocodone, oxycodone or hydromorphone)	59 (52.2)	34 (51.5)	25 (53.2)	1	30 (46.9)	29 (59.2)	0.268
Any intravenous/intranasal/oral opioid	111 (98.2)	66 (100.0)	45 (95.7)	0.171	62 (96.9)	49 (100.0)	0.504
Oral morphine milligram equivalents (MME) per kilogram body weight†	0.70 (0.37)	0.73 (0.35)	0.65 (0.40)	0.240	0.64 (0.37)	0.77 (0.38)	0.055
Received intravenous fluids	86 (76.1)	50 (75.8)	36 (76.6)	1	45 (70.3)	41 (83.7)	0.153
Laboratory values							
White blood cell count (X 10–9/L)	12.3 (4.8)	12.6 (4.8)	12 (4.9)	0.571	12.3 (4.7)	12.3 (4.9)	0.988
Hemoglobin (g/dL)	9.8 (1.8)	10.2 (1.9)	9.3 (1.4)	**0.011**	9.9 (2)	9.7 (1.3)	0.432
Platelets (X 10–9/L)‡	388.2 (176)	365.2 (162.7)	421.2 (190.5)	0.098	367.1 (172.9)	415.4 (178)	0.151
Admitted to hospital from ED (n, %)	52 (46.0)	31 (47.0)	21 (44.7)	0.961	22 (34.4)	30 (61.2)	**0.008**
Length of stay if discharged home from ED (mean [SD])	235.8 (72)	220.5 (70.2)	256.5 (70.3)	**0.052**	221.6 (71.6)	267.3 (63.6)	**0.020**

Hypothesis testing done by 2-sample *t* test with equal variance for continuous variables and χ^2 with Yates continuity correction/Fisher exact tests for categorical variables.

* n = 111.

† MME calculated up to assessment of the final pain score before 360 minutes or up to 360 minutes. Home methadone dosing not incorporated in calculation.

‡ n = 112.

HCU, health care utilization; NSAID, nonsteroidal anti-inflammatory drugs.

opioid analgesia was 36.2 minutes (SD 25.5), and there were no sex differences or differences by history of high HCU for pain. There were no differences in total dose of opioid analgesia per kilogram body weight administered in the ED between sex and history of high HCU for pain, although those with high HCU for pain were more likely to receive IV opioids ($P < 0.001$). More than half (n = 65, 57.5%) received IN fentanyl, 80.5% (n = 91) received IV ketorolac, 52.2% (n = 59) received PO opioids, almost all received an opioid medication (98.2%) and all received either an opioid or IV ketorolac. Most (n = 86, 76.1%) received IV fluids, with no differences based on sex or history of high HCU for pain.

Patients discharged home from the ED had a mean LOS of 235.8 minutes (SD 72). Amongst those discharged home, female patients had a trend towards longer LOS ($P = 0.052$) and those with high HCU for pain had a longer LOS ($P = 0.020$). Those with high HCU for pain were also more likely to be admitted to the hospital.

3.3. Longitudinal pain trajectories

The mean follow-up time of assessment of the last pain score (referent to the time of the first pain score) was 214.3 minutes (SD 73.2). The mean number of pain score assessments was 6.34 (SD 2.47). Although the follow-up time of assessment of the last pain score was longer amongst those with high HCU ($P = 0.019$), there were no significant differences in the number of pain score assessments in those with high HCU as compared with those with low HCU. Results from a bivariable linear mixed model, examining trend in pain score over time, found a significant decrease in pain score for the entire cohort, with an average 0.5-point drop for every 30 minutes (each 1-minute slope = −0.016, 95% CI: −0.018, −0.013, $P < 0.001$; **Table 3**, **Fig. 1A**). Similar models adjusting for MME (kg) alone and MME (kg) plus use of hydroxyurea each found a common relationship between follow-up time and pain scores (each 1-minutes slopes = −0.015 and −0.015, respectively, both $P < 0.001$; **Table 3**). Using this same base linear mixed model and adding both patient sex as a main effect and the statistical interaction between follow-up time and patient sex, the change in pain score over follow-up between male and female patients was found to be insignificant (male 1-minute slope = −0.017, female 1-minute slope = −0.015, $P = 0.511$; **Table 4**, **Fig. 1B**). After adjustment for MME (in kilograms) alone and MME (in kilograms) plus hydroxyurea, the statistical interactions between follow-up time and patient sex remained insignificant ($P = 0.508$ and $P = 0.509$ respectively; **Table 4**). Implementing these same methods, and substituting patient sex with HCU, the change in pain score over follow-up between low HCU and high HCU was found to be significant (low HCU 1-minute slope = −0.019, high HCU 1-minute slope = −0.011, $P = 0.001$; **Table 5**, **Fig. 1C**). After adjustment for MME (in kilograms) alone and

Table 3

All results unadjusted and adjusted for (1) morphine milligram equivalents (in kilograms) and (2) morphine milligram equivalents (in kilograms) and hydroxyurea.

Effect	Unadjusted β (95% CI)	*P*	Adjusted 1 β (95% CI)	*P*	Adjusted 2 β (95% CI)	*P*
Intercept	7.49 (7.11, 7.86)	**<0.001**	5.88 (5.14, 6.62)	**<0.001**	5.68 (4.84, 6.53)	**<0.001**
Follow-up (min)	−0.016 (−0.018, −0.013)	**<0.001**	−0.015 (−0.018, −0.013)	**<0.001**	−0.015 (−0.018, −0.013)	**<0.001**
MME (kg)	—	—	2.28 (1.35, 3.21)	**<0.001**	2.37 (1.42, 3.31)	**<0.001**
Hydroxyurea						
No	—	—	—	—	0.38 (−0.35, 1.12)	0.305
Yes	—	—	—	—	Reference	

95% CI, 95% confidence interval; MME, morphine milligram equivalents.

MME (in kilograms) plus hydroxyurea, the statistical interactions between follow-up time and HCU remained significant (both $P = 0.001$; **Table 5**). Finally, retaining both patient sex and HCU as main effects, and considering the 3-way interaction between patient sex, HCU, and follow-up, a significant interaction was found with female-low HCU as having the steepest slope in pain score over follow-up (1-minute slope = −0.021), followed by male-low HCU (1-minute slope = −0.019) and male-high HCU (1-minute slope = −0.013). Female-high HCU had the flattest slope (1-minute slope = −0.009), meaning that their change in pain scores over follow-up was the least of the 4 patient combinations. The trajectory for female-high HCU was significantly different from female-low HCU and male-low HCU (both $P = 0.005$; **Table 6**, **Fig. 1D**). After adjustment for MME (in kilograms) alone and MME (in kilograms) plus hydroxyurea (both statistically significant), the same statistical interactions

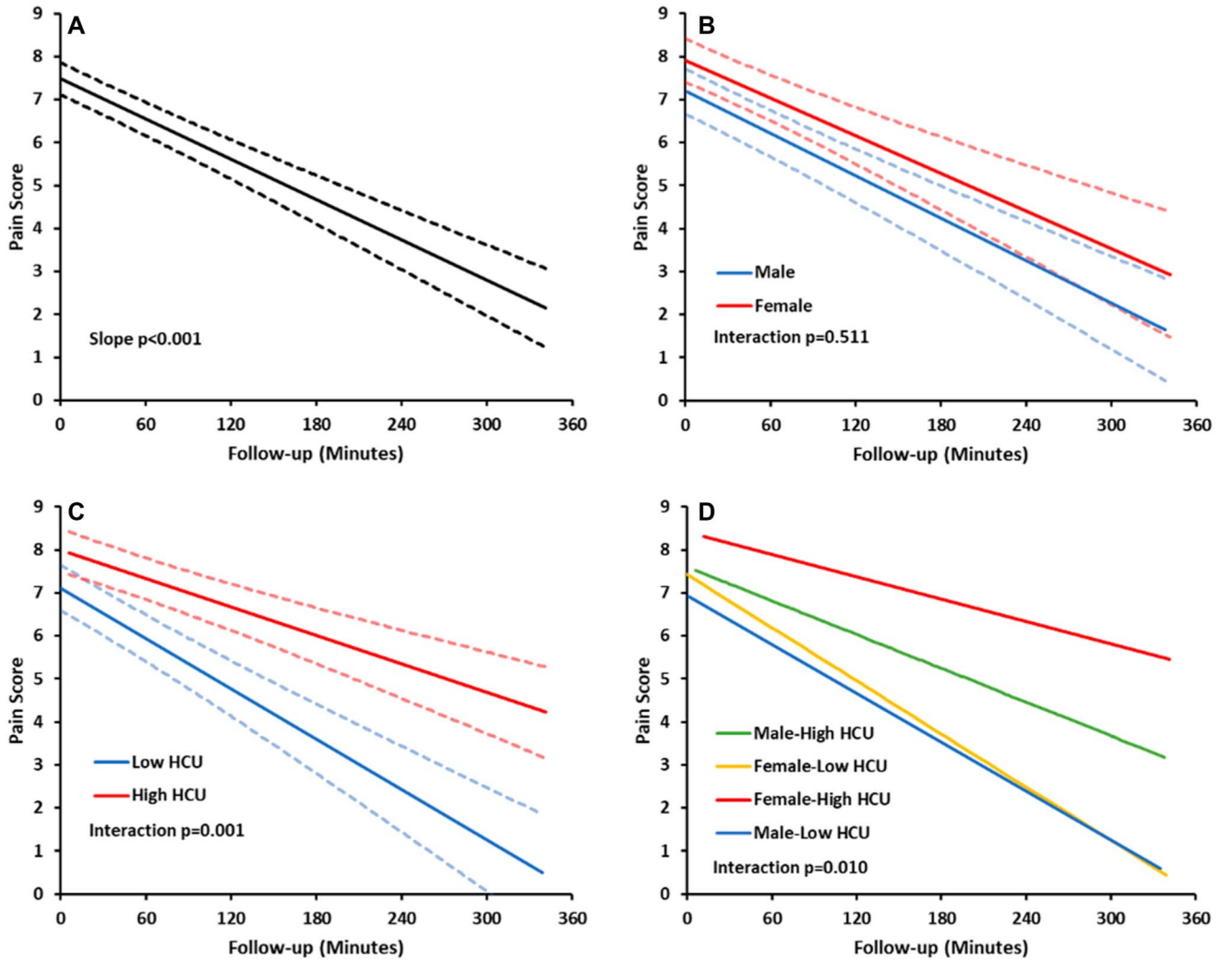

Figure 1. (A) Unadjusted trends in pain score over follow-up with 95% CI. (B) Unadjusted trends in pain score over follow-up by sex, with interaction of slopes *P* value and 95% CI. (C) Unadjusted trends in pain score over follow-up by health care utilization, with interaction of slopes *P* value and 95% CI. (D) Unadjusted trends in pain score over follow-up by sex and health care utilization, with interaction of slopes *P* value. 95% CI, confidence interval; HCU, health care utilization.

Table 4

Results by sex, unadjusted and adjusted for (1) morphine milligram equivalents (in kilogram) and (2) morphine milligram equivalents (in kilogram) and hydroxyurea.

Effect	Unadjusted β (95% CI)	P	Adjusted 1 β (95% CI)	P	Adjusted 2 β (95% CI)	P
Intercept	7.91 (7.40, 8.42)	**<0.001**	6.36 (5.57, 7.15)	**<0.001**	6.14 (5.26, 7.02)	**<0.001**
Follow-up (min)	−0.015 (−0.019, −0.010)	**<0.001**	−0.014 (−0.019, −0.010)	**<0.001**	−0.014 (−0.019, −0.010)	**<0.001**
Sex						
Male	−0.72 (−1.45, 0.002)	0.051	−0.91 (−1.61, −0.21)	**0.011**	−0.94 (−1.64, −0.24)	**0.009**
Female	Reference		Reference		Reference	
Follow-up × sex						
Male	−0.002 (−0.007, 0.004)	0.511	−0.002 (−0.007, 0.004)	0.508	−0.002 (−0.007, 0.004)	0.509
Female	Reference		Reference		Reference	
MME (kg)	—	—	2.36 (1.45, 3.27)	**<0.001**	2.48 (1.54, 3.42)	**<0.001**
Hydroxyurea						
No	—	—	—	—	0.43 (−0.30, 1.16)	0.250
Yes	—	—	—	—	Reference	

95% CI, 95% confidence interval; MME, morphine milligram equivalents.

remained significant (**Table 6**). Specifically, compared with the referent slope for female-high HCU, the slope for female-low HCU was 2.5 times greater (−0.020 vs −0.008) and for male-low HCU, it was 2.25 times greater (−0.018 vs −0.008).

4. Discussion

This study represents a detailed examination of acute pain and acute pain trajectories in a large sample of adolescents with SCD who present to the ED, by sex and history of pain frequency as measured by HCU for pain.

We did not find a difference between male and female adolescents in their initial pain intensity in the ED during an acute pain episode, consistent with the lack of sex differences in mean pain intensity during crises in the Pain in Sickle Cell Epidemiology Study (PiSCES).[17] We did not find sex differences in the total dose of opioid analgesia per kilogram body weight administered in the ED. This may reflect treating physicians' high fidelity to standardized protocols for the treatment of acute pain in the ED at our center. This contrasts with the Multicenter Study of Hydroxyurea, where male patients with SCD received higher doses of opioids as compared with female patients, both in the outpatient and the inpatient setting, although this comparison was not adjusted by weight.[2]

We found that adolescents with high HCU for pain reported a statistically significant higher pain score at presentation to the ED. This study also indicates that both sex and history of high HCU for pain are associated with longitudinal trajectories of pain intensity during presentation for an acute painful episode to the ED. Those with history of high HCU for pain had, on average, a slower decline in pain intensity. Although we did not find an effect of sex alone on pain trajectories, models incorporating both sex and history of high HCU indicated a significant interaction between sex and history of high HCU for pain over follow-up time. Female patients with high HCU, on average, appeared to have the slowest decline in pain intensity. These results are consistent with a previous report examining acute pain trajectories in SCD, which indicated that hospitalizations among female patients or among those with more frequent complications of SCD were associated with a slower decline in pain intensity.[25] However, in retrospective studies, including this study, acute pain trajectories were examined after presentation to the ED, and the effect of duration of pain experienced at home prior to presentation to the ED on observed pain trajectories in an acute care setting could not be assessed. In addition, although we could not definitely assess for history of chronic pain in this retrospective study, it is likely that some individuals with high HCU also had chronic pain, and the impact of history of chronic pain on pain trajectories could not be

Table 5

Results by health care utilization, unadjusted and adjusted for (1) morphine milligram equivalents (in kilogram) and (2) morphine milligram equivalents (in kilograms) and hydroxyurea.

Effect	Unadjusted β (95% CI)	P	Adjusted 1 β (95% CI)	P	Adjusted 2 β (95% CI)	P
Intercept	7.99 (7.49, 8.49)	**<0.001**	6.35 (5.49, 7.21)	**<0.001**	6.10 (5.20, 7.01)	**<0.001**
Follow-up (min)	−0.011 (−0.014, −0.008)	**<0.001**	−0.011 (−0.014, −0.008)	**<0.001**	−0.011 (−0.014, −0.008)	**<0.001**
HCU						
Low	−0.88 (−1.60, −0.16)	**0.018**	−0.58 (−1.29, 0.12)	0.105	−0.78 (−1.52, −0.04)	**0.039**
High	Reference		Reference		Reference	
Follow-up × HCU						
Low	−0.008 (−0.013, −0.003)	**0.001**	−0.008 (−0.013, −0.003)	**0.001**	−0.008 (−0.013, −0.003)	**0.001**
High	Reference		Reference		Reference	
MME (kg)	—	—	2.09 (1.18, 3.00)	**<0.001**	2.25 (1.33, 3.18)	**<0.001**
Hydroxyurea						
No	—	—	—	—	0.67 (−0.09, 1.44)	0.084
Yes	—	—	—	—	Reference	

95% CI, 95% confidence interval; HCU, health care utilization; MME, morphine milligram equivalents.

Table 6

Results by sex and health care utilization, unadjusted and adjusted for (1) morphine milligram equivalents (in kilogram) and (2) morphine milligram equivalents (in kilogram) and hydroxyurea.

Effect	Unadjusted β (95% CI)	P	Adjusted 1 β (95% CI)	P	Adjusted 2 β (95% CI)	P
Intercept	8.42 (7.81, 9.03)	**<0.001**	6.72 (5.77, 7.66)	**<0.001**	6.50 (5.52, 7.48)	**<0.001**
Follow-up (min)	−0.009 (−0.014, −0.004)	**0.002**	−0.008 (−0.014, −0.003)	**0.003**	−0.008 (−0.014, −0.003)	**0.002**
Sex-HCU						
Male-low HCU	−1.49 (−2.41, −0.56)	**0.002**	−1.34 (−2.26, −0.41)	**0.005**	−1.61 (−2.56, −0.65)	**0.001**
Male-high HCU	−0.82 (−1.79, 0.15)	0.096	−0.95 (−1.90, −0.002)	**0.049**	−1.04 (−2.03, −0.06)	**0.039**
Female-low HCU	−1.00 (−1.98, −0.02)	**0.046**	−0.57 (−1.61, 0.47)	0.276	−0.86 (−1.93, 0.21)	0.111
Female-high HCU	Reference		Reference		Reference	
Follow-up × sex-HCU						
Male-low HCU	−0.010 (−0.017, −0.003)	**0.005**	−0.010 (−0.017, −0.003)	**0.005**	−0.010 (−0.017, −0.003)	**0.005**
Male-high HCU	−0.004 (−0.011, 0.002)	0.173	−0.004 (−0.011, 0.002)	0.174	−0.004 (−0.011, 0.002)	0.169
Female-low HCU	−0.012 (−0.020, −0.004)	**0.005**	−0.012 (−0.020, −0.004)	**0.005**	−0.012 (−0.020, −0.004)	**0.005**
Female-high HCU	Reference		Reference		Reference	
MME (kg)	—	—	2.26 (1.36, 3.16)	**<0.001**	2.43 (1.52, 3.34)	**<0.001**
Hydroxyurea						
No	—	—	—	—	0.78 (0.01, 1.54)	**0.046**
Yes	—	—	—	—	Reference	

95% CI, 95% confidence interval; HCU, health care utilization; MME, morphine milligram equivalents.

assessed. These factors should be explored further in prospective studies, particularly in studies that determine the response to analgesics in clinical trials of acute pain in SCD, which may enroll a substantial proportion of participants with high prior HCU for pain or with chronic pain.

In this study, we did not find any sex differences in the rates of admission to the hospital but, among those discharged home, did find that female patients had a trend towards longer LOS in the ED. As we only examined LOS amongst those discharged from the ED, we cannot comment on whether LOS was high in female patients overall, if inpatient LOS had also been considered. It is not clear if LOS is higher in female adolescents with SCD,[8,9] but among adults, female patients account for a higher percentage of inpatient visits than adult male patients,[11] and adult female patients with HbSS have a longer mean inpatient LOS as compared with adult male patients with or without HbSS, regardless of age.[11] We also found that those with prior high HCU for pain had a longer LOS in the ED even when discharged home and overall were more likely to be admitted for continuing pain management.

Although female patients have a higher prevalence of chronic pain conditions as compared with male patients,[3] it is unclear whether female patients experience a greater pain burden in SCD. In the Cooperative Study of SCD (CSSCD), sex was an independent predictor of pain rates in a multivariable Poisson model adjusted for age, hematocrit, and fetal hemoglobin levels, with higher rates of pain in female patients compared with male patients.[23] In the newborn cohort of the CSSCD, which prospectively followed children from birth for 10 years, female children with HbSS experienced higher rates of painful crises compared with male children with HbSS.[10] Another retrospective review suggested that there was a higher proportion of female patients with SCD with high HCU (defined a ≥4 episodes in that study) as opposed to the low HCU.[4] However, in PiSCES, which collected out-of-hospital pain diary data, there were no sex differences in the number of pain days or pain episodes or in the mean pain intensity during crisis after controlling for age, education, genotype, and depression,[17] but men with HbSS genotype reported increased percentage of days with crisis and a trend towards higher utilization as compared with women.[17] The authors in the PiSCES study postulated that these lack of sex differences in overall pain burden may be the result of differences because of race or life experiences with SCD.[17] In a more recent cohort, Lanzkron et al.[16] did not find any differences in acute care utilization for pain between male and female patients in a univariate model among adults with SCD followed for 1 year in the "Examining Sickle Cell Acute Pain in the Emergency vs Day Hospital" (ESCAPED) trial. However, the effect of sex was not explored in a multivariable model in this study, and, unlike earlier cohorts, almost 70% of participants in this study reported chronic daily pain.[16] In examining complications of SCD associated with pain, we did not find that the prevalence of known AVN was different by sex or by history of high HCU for pain, but our sample is smaller than prior studies, which indicates higher rates of AVN among those who have high HCU[4] or chronic pain.[16] It is possible that not all individuals with AVN in this cohort were diagnosed and/or had radiographic data. Thus, the effect of sex on acute and chronic pain deserves further prospective study, and the effect of age (adults compared with children) should also be further examined. In addition, in line with recent recommendations,[20] future studies investigating sex-specific effects should incorporate study of female sex–specific questions such as the temporal association of menstrual cycles and SCD pain, as well as the impact of interventions such as hormonal contraception on SCD acute and chronic pain.

Notably, 43% of the patients in this cohort had 3 or more visits per year for pain. We cannot draw conclusions regarding the high proportion of patients with high HCU in this study because this likely reflects our selection criteria, which may have biased our sample toward patients with higher HCU for pain. We also found that patients with high HCU were more likely to be prescribed disease-modifying therapies like HU, which may reflect the increased prescription of HU to patients with more severe disease, as has been previously described.[26] Finally, the higher BMI seen in the group with higher HCU was not fully explained and may be confounded by increased use of HU in this group and unmeasured variables such as disease severity.[5] Previous reports are mixed in the association of BMI and frequency of hospitalization in SCD,[28,29] but the association of BMI with pain frequency should be evaluated in future studies, accounting for all confounding factors.

Strengths of this study include a relatively large sample of adolescents with SCD. Although this was conducted at a single institution, patients were seen at 3 different campuses and the multicampus nature of our institution adds to the generalizability of this study. Another strength was the examination of longitudinal pain trajectories in the ED, which allowed us to study the trajectories of pain intensity in the first few hours of presentation to the ED. To our knowledge, this is the first description of acute pain and longitudinal pain trajectories in adolescents with SCD, examining the influence of sex and prior HCU for pain.

This study had some limitations. Despite the multicampus nature of this single institution study, it is possible that some of our findings reflect institutional practice and may not be generalizable. We excluded ED visits for which patients received analgesics from emergency medical services or treatment at an outside hospital before arrival at the ED. However, this may have inadvertently excluded episodes with more severe pain. It also may have disproportionately excluded patients living further away from our centers who first sought care at another facility. As we were studying response to analgesia, we also excluded visits where patients received an analgesic in our ED or enroute to ED through EMS before the first pain score was recorded, and it is possible that this may have biased the sample toward patients presenting with less severe presenting pain. In addition, evaluation of prior HCU for pain was limited to care sought at our center and not at other facilities, which may have contributed to underestimation of prior HCU for pain. Because we only collected pain-associated variables and SCD pain–associated comorbidities like AVN, we could not ascertain if other SCD comorbidities were associated with any outcomes of interest in this study. As prescription medications were abstracted from the EHR, the adherence to medications such as hydroxyurea could not be verified, and the use of over-the-counter medications for pain could not be ascertained. Given the retrospective nature of this study, the history of chronic pain per published AAPT criteria[6] for chronic pain in SCD could not be ascertained, but it is likely that at least some individuals with high HCU for pain experienced chronic pain associated with SCD. Our findings should be further investigated in prospective studies examining individual differences in acute pain in SCD, particularly in those with chronic SCD pain.

5. Conclusions

Sex and history of high HCU for pain are associated with acute pain trajectories in adolescents with SCD presenting to the ED. These novel findings should be confirmed in future prospective studies.

Disclosures

CRM is the Executive Director of Food as Medicine Therapeutics, LLC; and is on the scientific advisory Board for Trility. CRM is the inventor or co-inventor of several UCSF-Benioff Children's Hospital Oakland patents/patent-pending applications that include nutritional supplements for autism/apraxia (receiving royalties); is an inventor or co-inventor of several Emory University School of Medicine patent application for nutritional supplements for autism, and coronaviruses, and kidney disease and is a consultant for Roche and CSL Behring, and an editor for the sickle cell disease-fever reference for UpToDate.

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