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Pain and opioid use after reversal of sickle cell disease following HLA-matched sibling haematopoietic stem cell transplant

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sickle cell disease; haematopoietic stem cell transplant; pain; opioids

The burden of pain varies among patients with sickle cell disease (SCD). Chronic pain, resulting from multiple aetiologies, is common in SCD. The Analgesic, Anaesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy (ACTTION-AAPT) criteria have recently described subcategories of chronic SCD pain (Dampier *et al*, 2017). Haematopoietic stem cell transplant (HSCT) is the most accessible curative therapy for SCD resulting in disease-free survival in over 85% (Hsieh *et al*, 2014; Gluckman *et al*, 2017). After successful HSCT (as

Author contributions

Performed the research: DSD, JL, AI, SM, MR, CDF, JFT, SLT, MH. Designed the research study: DSD, JL, SLT, JFT, MH. Analysed the data: DSD, JL, MH. Wrote the paper and approved the final version of the manuscript: DSD, JL, AI, SM, MR, CDF, JFT, SLT, MH.

*DSD and JL contributed equally to this work.

Competing interests

None.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. Pre-HSCT characteristics associated with pain requiring opioid therapy 12 months after reversal of SCD following HSCT in the patients with PROMIS data ($n = 20$).

defined by haematological parameters), most patients are weaned off opioids; however, a subgroup of patients continues to experience pain that requires opioid treatment.

We determined the prevalence and correlates of pain requiring continued opioid treatment at 12 months after successful non-myeloablative human leucocyte antigen-matched sibling allogeneic HSCT in a cohort of SCD patients (Fig 1) (Hsieh *et al*, 2014). The Institutional Review Board of the National Institutes of Health approved the protocol. All participants provided informed consent. Detailed data on the clinical course, pain, opioid use and laboratory values were prospectively collected within 3 months prior to HSCT and at 12 months post-HSCT ($n = 35$). Patient Reported Outcomes Measurement Information System (PROMIS) measures were also prospectively collected at the same time points in a subgroup of these patients ($n = 20$). The PROMIS domains assessed included pain intensity, pain impact, anxiety, depression, satisfaction with social role, physical function, fatigue and sleep disturbance (Cella *et al*, 2007; Keller *et al*, 2017). All PROMIS raw data were converted to T-scores.

Based on pain history pre-HSCT, patients reporting chronic pain were classified using AAPT guidelines (Dampier *et al*, 2017) into one of following three chronic pain subtypes: (i) AAPT subtype 1 - chronic pain *without* contributory SCD complications (e.g. avascular necrosis or leg ulcers), (ii) AAPT subtype 2 - chronic pain *with* evidence of contributory SCD complications based on clinical signs or test results (iii) AAPT subtype 3 - chronic pain with *mixed* pain types if there was evidence of contributory SCD complications and also pain in unrelated sites (e.g. arms, back, chest or abdominal pain). Patients who only experienced acute episodic pain were grouped separately (Episodic pain only) (Fig 1). Non-parametric statistical analysis was performed using IBM SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for windows, version 24 0. Armonk, NY: IBM Corp). Given the limited sample size, descriptive statistics were reported primarily. When direct statistical comparisons were required, Independent samples Mann-Whitney U or Chi-squared Tests were used.

The median age of the cohort was 32 years (range: 16– 65 years) and 21 (60%) patients were male. Pre-HSCT (Fig 1), all patients had experienced intermittent episodes of acute pain; 16 (46%) had acute episodic pain only, 4(11%) also had chronic pain without SCD complications (AAPT-1), 9 (26%) also had chronic pain with contributory SCD complications (AAPT-2) and 6 (17%) also had mixed pain phenotype (AAPT-3). Post-HSCT, haematological parameters improved in all patients (Table I) (Hsieh *et al*, 2014). Median pain-related admissions decreased significantly [from 3 admissions/year (range 0–24) pre- HSCT to 0 (range 0–3) post-HSCT; ($P < 0.001$)]. Overall, there was significant reduction in the prescription of both short- and long-acting opioids pre-vs. post-HSCT (91% to 40% for short-acting and 40% to 14% for long-acting opioids; $P < 0.001$). At 12 months post-HSCT, 14 of 35 (40%) patients reported persistent pain requiring opioids. Examination of continued opioid use patterns, showed that all four patients (100%) in AAPT-1 and five of six (83%) in AAPT-3, continued to use opioids to manage their pain while 4 of 9 patients (44%) in AAPT-2 and all patients in the Episodic pain only group stopped using opioids post-HSCT (Table I).

Analysis of pre- and post-HSCT PROMIS data in a subgroup of patients ($n = 20$) showed significant improvement in the subscales of pain intensity ($P = 0.03$), pain impact ($P = 0.007$), satisfaction with social role ($P = 0.03$) and physical function ($P = 0.004$) following HSCT. No significant changes were seen for fatigue ($P = 0.09$), anxiety, depression or sleep disturbance, which could be related to small sample size (Table II). However, when comparing patients with persistent pain post-HSCT (AAPT-1 and AAPT-3) ($n = 6$) versus those with resolved pain post-HSCT ($n = 8$), pre-HSCT anxiety ratings were significantly higher in the group with unexplained, persistent pain ($P = 0.05$). Additional pre-HSCT factors that were associated with unexplained, persistent pain post-HSCT included higher burden of pain as defined by higher median pain admissions/year (2 (0–10) vs. 5 5 (3–9); $P = 0.04$); higher overall numerical pain rating on a 0–10 scale [2 (0–5) vs. 6 (5–7); $P = 0.02$] and treatment with long acting opioids (0% vs. 83%; $P < 0.001$) (Table S1).

Successful HSCT leads to resolution of pain in the large majority of SCD patients. Pre-HSCT characteristics of the subgroup of patients reporting persistent pain/opioid use post-HSCT included older age (33 5 vs. 22 5 years; $P =$ not significant), significantly higher pain burden (more pain admissions and higher pain intensity ratings), more symptoms of anxiety and more probable use of long-acting opioids pre-HSCT. Utilizing AAPT chronic pain subtypes in SCD, our analysis also shows that pain outcomes post-HSCT may be influenced by pre-HSCT pain characteristics. In our cohort, patients with persistent pain were more likely to have chronic pain *without* contributory SCD complications or the *mixed* pain phenotype pre-HSCT. These findings confirm the complex neurobiology of pain in SCD, where different mechanisms may contribute to pain (Darbari *et al*, 2014). Interestingly, while none of our patients on short-acting opioids experienced continued pain, use of long-acting opioids was associated with continued pain. This may be a reflection of more severe disease in this group; however, contributions from other factors, such as opioid-induced hyperalgesia, central sensitization or genetic predisposition cannot be ruled out (Campbell *et al*, 2016; Carroll *et al*, 2016).

The strengths of this transplant cohort include prospective longitudinal surveys of pain and quality of life analyses pre- and post-HSCT compared to previous studies (Beverung *et al*, 2015; Walters *et al*, 2016). Additionally, our cohort suffered no acute or chronic graft-versus-host disease (GvHD), thus the burden of pain was not confounded by GvHD. Limitations of the study include lack of mechanistic studies and a follow-up period limited to 12 months post-HSCT. Nonetheless, our study provides the rationale for addressing clinical and psychological comorbidities pre-HSCT, and even considering HSCT at a younger age before development of these complications, to improve outcomes post-HSCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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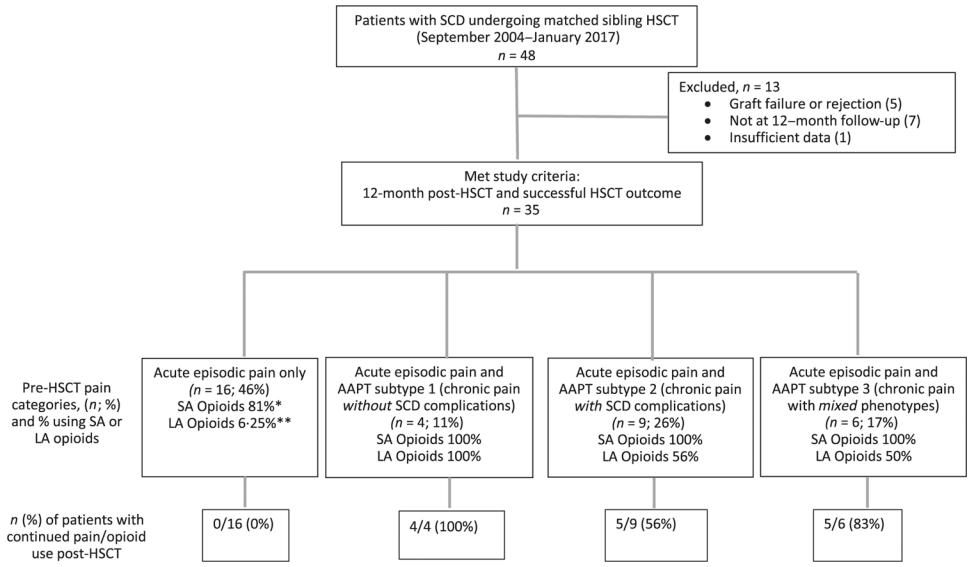

Fig 1.

Opioid use pre- and post-HSCT by AAPT pain categories. *3 patients in acute episodic pain group had not reported using opioids. **1 patient in acute episodic pain group was on long acting opioids intermittently. AAPT, ACTTION-American Pain Society Pain Taxonomy diagnostic criteria for chronic SCD pain; AAPT subtype 1, Chronic SCD pain *without* contributory disease complications was used if there was no evidence of contributory SCD complications based on either clinical signs (e.g., presence of leg ulcers) or test results (e.g., imaging abnormalities); AAPT subtype 2, Chronic SCD pain with contributory disease complications was used if there was evidence of contributory SCD complications based on clinical signs or test results; AAPT subtype 3, Chronic SCD pain with *mixed* pain types was used if there was evidence of contributory SCD complications (e.g., avascular necrosis) based on clinical signs or test results and there was also pain occurring in unrelated sites (e.g., arms, back, chest, or abdominal pain); HSCT, hematopoietic stem cell transplant; LA Opioids, Long acting opioids; SA Opioids, Short acting opioids; SCD, sickle cell disease.

Table I.

Pre- and one-year post-HSCT patient characteristics including chronic pain categories by AAPT criteria pre-HSCT (*n* = 35).

	Acute episodic pain only (*n* = 16)		**Chronic pain *without* SCD complications (AAPT subtype 1) (*n* = 4)**		**Chronic pain *with* SCD complications (AAPT subtype 2) (*n* = 9)**		**Chronic pain with *mixed* pain phenotype (AAPT subtype 3) (*n* = 6)**	
Age at HSCT (years)	25 (16—41)		34–5 (23–65)		36 (22–53)		34 (19–47)	
Gender	6 F + 10 M		3 F + 1 M		2 F + 7 M		3 F + 3 M	
Hydroxycarbamide pre-HSCT (mg)	1250 (500–2500)		2000 (1500–2500)		1500 (1000–2000)		1750 (500–2000)	
	Pre-HSCT	**Post-HSCT**	**Pre-HSCT**	**Post-HSCT**	**Pre-HSCT**	**Post-HSCT**	**Pre-HSCT**	**Post-HSCT**
Admissions for pain/year *n* (range)	2 (0–24)	0 (0)	6 (3–9)	0–5 (0–2)	2 (0–10)	0 (0)	4–5 (3–15)	0 (0–3)
Short–acting opioids use *n* (%)	13/16 (81%)	0 (0)	4/4 (100%)	4/4 (100%)	9/9 (100%)	5/9 (56%)	6/6 (100%)	5/6 (83%)
Long-acting opioids use *n* (%)	1/16 (6–25%)	0 (0)	4/4 (100%)	1/4 (25%)	5/9 (56%)	1/9 (11%)	3/6 (50%)	3/6 (50%)
Haemoglobin (g/1)	92 (72–105)	135 (102–168)	90 (74–92)	106 (72–126)	83 (67–105)	142 (99–195)	88 (77–98)	119 (105–135)
Donor red cell phenotype achieved	N/A	Yes	N/A	Yes	N/A	Yes	N/A	Yes

AAPT, ACTTION- American Pain Society Pain Taxonomy; HSCT, haematopoietic stem cell transplant; N/A, not applicable; SCD, sickle cell disease. Data displayed as median and range.

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Table II.

Pre- and post-HSCT comparison of PROMIS measures (T-scores; $n = 20$).

PROMIS Measures (n = 20)	Pre–HSCT	Post–HSCT	Post–HSCT outcome
Pain intensity (NRS 0–10) *	4.5 (0–8)	0.5 (0–7)	Improved ($P < 0.05$)
Pain impact *	59.9 (40.7–77)	40.7 (34.9–77)	Improved ($P < 0.05$)
Physical functionf †	43.5 (32–59.2)	59.2 (32–59.2)	Improved ($P < 0.05$)
Satisfaction with social role †	50 (26.9–66.1)	55.7 (30.8–66.1)	Improved ($P < 0.05$)
Fatigue *	53 (33.1–65.3)	42.7 (33.1–72.4)	Unchanged (trend towards improvement, $P = 0.09$)
Anxiety *	49.4 (37.1–66.6)	44.6 (37.1–74.1)	Unchanged (n/s)
Depression *	46.1 (38.2–64.9)	46.1 (30.5–81.3)	Unchanged (n/s)
Sleep disturbance *	53.4 (30.5–77.6)	47.9 (30.5–74.1)	Unchanged (n/s)

HSCT, haematopoietic stem cell transplant; NRS, numeric rating scale; PROMIS, patient reported outcome measures information system.

* Higher scores in these measures indicate more suffering.

† Higher scores in these measures indicate better health.

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