HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2023 January 06.

Published in final edited form as:

Pediatr Blood Cancer. 2023 January ; 70(1): e30046. doi:10.1002/pbc.30046.

Multimodal phenotyping and correlates of pain following hematopoietic cell transplant in children with sickle cell disease

Nitya Bakshi[1,2], **Rachel Astles**[3], **Eric Chou**[4], **Asha Hurreh**[5], **Soumitri Sil**[1,2], **Cynthia B Sinha**[1,2], **Kolanda Ackey Sanders**[2], **Manasa Peddineni**[6], **Scott E Gillespie**[7], **Rohali Keesari**[7], **Lakshmanan Krishnamurti**[1,2]

[1]Division of Pediatric Hematology-Oncology-BMT, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA

[2]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, Georgia, USA

[3]Emory University School of Medicine, Atlanta, Georgia, USA

[4]Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

[5]James T. Laney School of Graduate Studies, Emory University, Atlanta, Georgia, USA

[6]Nova Southeastern University College of Osteopathic Medicine, Fort Lauderdale, Florida, USA

[7]Pediatric Biostatistics Core, Department of Pediatrics, Emory University, Atlanta, Georgia, USA

Abstract

Introduction: There is limited understanding of pain, patient-reported outcomes (PROs) of health-related quality of life (HRQoL), psychological factors, and experimental pain sensitivity before and following hematopoietic cell transplant (HCT) in children with sickle cell disease (SCD).

Methods: Individuals aged 8 years and older, English speaking, and scheduled for a HCT were invited to participate in an observational study where they completed assessments of pain, PROs, psychological factors, and qualitative interviews before and around 3 months, 6 months, 1 year, and 2 years post-HCT. An optional substudy of experimental pain sensitivity before and around 6 month, 1 year, and 2 years post-HCT was also offered.

Results: Data from eight participants (median age 13.5 years, 25% female) with sickle cell anemia (SCA) or similarly severe genotype, and successful donor-derived erythropoiesis post-

Correspondence: Nitya Bakshi, Division of Pediatric Hematology-Oncology-BMT, Department of Pediatrics, Emory University, Atlanta, GA; Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, GA; 2015 Uppergate Drive, Atlanta, GA 30322, USA. nitya.bakshi@emory.edu.

CONFLICT OF INTEREST

The author(s) declare that they have no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

HCT are reported. We found that collection of pain, PROs, psychological factors, and qualitative data were feasible in the context of HCT. We found moderate to large differences in pain and some PROs between baseline to 1 year and baseline to 2 year post-HCT based on effect sizes, but only some differences were statistically significant. We found moderate to large differences in pressure pain threshold and moderate differences in cold pain threshold between baseline to 1 year and baseline to 2 year post-HCT based on effect sizes, but these differences were not statistically significant. Qualitative data indicated an improvement in pain and HRQoL post-HCT.

Conclusion: This study provides a framework for the conduct of multimodal pain assessments before and after HCT, which is feasible but faced with unique barriers.

Keywords

pain; patient-reported outcomes; pediatric hematology/oncology; quality of life; sickle cell disease; transplantation

1 | INTRODUCTION

Pain is the hallmark of sickle cell disease (SCD) and is a significant cause of morbidity in SCD.[1] Hematopoietic cell transplantation (HCT) is a curative therapy for SCD,[2] and recurrent SCD pain episodes are a common indication for HCT.[3] Pain is also a frequent consideration in the decision to pursue HCT.[4] After successful HCT, resolution of pain in adults with SCD is a gradual process which may take a year or more following HCT.[5] For adults with chronic pain associated with SCD, pain may not resolve by a year after transplant and may persist despite successful HCT.[6] Similarly, pain and health-related quality of life (HRQoL) improve following HCT,[7] though there is variability in HRQoL in response to HCT.[7–10] Thus, change in pain and its characteristics after successful HCT serves as a unique model system to investigate the reversal of the pain state in SCD. The insights gained from such a study may shed light on the multiple factors associated with the pain experience in SCD.

There is limited understanding of pain, psychological comorbidities associated with pain and HRQoL following transplantation for SCD. This study aimed to determine the feasibility and acceptability of collecting data on pain, patient-reported outcomes (PROs), HRQoL and experimental pain sensitivity using quantitative sensory testing (QST), and to compare these before and following HCT in patients with SCD. We hypothesized that there would be a decrease in pain burden following HCT and improvement in pain-associated psychological comorbidity.

2 | METHODS

We invited patients with SCD who were aged 8 years and older, English speaking, and scheduled for an HCT to participate in this observational cohort study. Potential participants were required to be able to access the internet via a smartphone or a computer to complete an electronic pain diary. If they did not have access to the internet, they could participate in all aspects of the study except for the pain diary. Potential participants were excluded if

they had severe medical comorbidities or cognitive difficulties that would potentially limit understanding of study procedures, as determined by the primary investigator.

We collected data at five timepoints: pre-HCT, post-HCT days 90, 180, 365, and 2 years. The pre-HCT study assessments were done up to 12 weeks before the scheduled HCT. To limit missing data post-HCT and increase flexibility for participants, study assessments were performed up to 30 days prior or 60 days after post-HCT day 90, up to 60 days prior or 60 days after post-HCT day 180, up to 60 days prior or 90 days after post-HCT day 365, and up to 90 days before or after 2 years post-HCT. Study visits were scheduled to coincide with clinical care as much as possible. Participants were asked to complete assessments of pain, pain-related PROs, psychological factors, functioning, and HRQoL, an electronic multidimensional pain diary and a qualitative interview at each timepoint. Study participants were also offered enrollment on to an optional substudy of experimental pain using QST performed at all times except at the day 90 timepoint as the other procedures.

2.1 | Assessments of pain, pain-related PROS, psychological characteristics, functional outcomes, and HRQoL

Participants were asked to complete the following measures:

1. Patient-Reported Outcomes Measurement Information System (PROMIS) short-form measures of pain intensity, pain interference, physical function, anxiety, depression, fatigue, sleep disturbance, and peer relationships. Most pediatric PROMIS measures have been previously validated and used in SCD[11–13] to measure pain, pain-related interference, and pain-related outcomes. PROMIS measures use a 7-day recall, and yield a T-score, which is a standardized score, and higher scores indicate greater presence of trait.
2. Pain Catastrophizing Scale (PCS),[14] a 13-item measure that measures thoughts and feelings about pain catastrophizing, and the child/adult version was used in this study. The PCS has high internal consistency in children with SCD.[15] Scores range from 0 to 52, and higher scores indicate greater pain catastrophizing.
3. Functional Disability Inventory (FDI)[16–18] is a well-established measure that evaluates perceived difficulty to perform daily activities across home, school, recreational, and social settings in youth with chronic pain, and the FDI has high internal consistency in children with SCD.[19] Scores range from 0 to 60, and higher scores indicate greater disability.
4. PedsQL™ Generic Quality of Life (QoL)[20–26] and PedsQL™ SCD Specific QoL[27–29] scales are valid and reliable measures that assess generic and SCD-specific HRQoL, respectively. These measures use a recall period of 1 month. Scores range from 0 to 100 and higher scores indicate better HRQoL.

All measures were obtained by child self-report. Participants received $25 at each timepoint for completion of the questionnaires.

2.2 | Multidimensional pain diary

Participants were asked to complete a twice daily web-based electronic multidimensional pain diary validated for measuring pain in SCD for 2 weeks using their smartphone or computer.[30] Participants reported their pain intensity on an 11-point numerical rating scale from 0 to 10. If a pain intensity score >0 was reported, they then were asked to report on cause of pain, pain impact on sleep, school, work, daily activities, interactions with friends and family, and treatments for pain. Participants were compensated $0.50 for completing each pain diary, for up to $1/day and $14 for each 2-week period.

2.3 | Qualitative interviews

Participants were invited to participate in a qualitative interview. The interview script focused on their experience of pain, its impact on their life, and the role of their pain experience in the decision to pursue HCT. For post-HCT time points, we explored their perspectives on their posttransplant pain and quality of life. Participants were compensated $25 for completion of the qualitative interview at each timepoint. Parents were also invited to participate but did not receive any compensation.

2.4 | Experimental pain sensitivity (QST)

We evaluated sensitivity to pressure, mechanical, and thermal stimuli. For detection thresholds, participants indicated when they first felt the stimuli; for pain thresholds, participants indicated when they first felt pain; and for pain tolerance, indicated when they could no longer tolerate the pain. We measured pressure pain threshold (PPTh), pressure pain tolerance (PPTo), mechanical pain threshold (MPTh), mechanical pain tolerance (MPTo), cold detection threshold (CDT), cold pain threshold (CPTh), heat detection threshold (HDT), heat pain threshold (HPTh), and heat pain tolerance (HPTo). We[13,31] and others[32] have previously published methods to determine these QST parameters in children with SCD. To determine MPTh, as pinprick probes were unavailable, we used a series of Von-Frey filaments (Touch Test™ Sensory Evaluator) weighing 0.008–300 g, applied from the lowest to the highest weight to determine the pain threshold. If the participant did not perceive pain with the 300 g filament, this was entered as 300 g. We calculated the arithmetic mean of three pain thresholds to determine the final MPTh.[32] At the end of the QST session, participants completed the Gracely Box Scale,[33,34] a 21-point scale to rate pain intensity and unpleasantness, and the situational PCS[35] to measure catastrophizing in response to the QST session. Participants could stop QST procedures at any time or omit portions of the QST procedures if they so desired. The timing of QST was preferably >2 weeks from the last pain episode. If a patient had chronic pain, the timing of QST was based on patient readiness, and away from the time of an exacerbation of chronic pain as much as possible. Participants were compensated $50 for the completion of QST procedures at each time point.

2.5 | Clinical characteristics

Clinical characteristics were abstracted from the medical record. We collected pertinent SCD-related history such as genotype, prior healthcare utilization for pain, and complications and treatments for SCD and pain. Healthcare utilization for pain was

calculated by the sum of all Emergency Department visits and hospitalizations for SCD pain. HCT-related history included donor characteristics, presence of donor-derived erythropoiesis post-HCT, and presence of acute and chronic graft-vs-host disease (GvHD).

2.6 | Statistical analysis

We used descriptive statistics to report the feasibility of completing study procedures including QST. We used descriptive statistics to describe the clinical characteristics of the study sample, as well as to describe pre- and post-HCT assessments. Where feasible, measurements at 1 year post-HCT and 2 years post-HCT were compared with baseline using paired Wilcoxon signed-rank tests; moreover, due to small sample size, standardized effect sizes (ESs) were further calculated to quantify the paired differences. ESs were calculated by dividing the absolute Wilcoxon signed-rank statistic (Z) by the square root of the number of pairs, and interpreted as small (0.1), moderate (0.3), and large (0.5).

To analyze pain diary data, we calculated the number of days where participants completed at least one pain diary; if only one of the two daily diaries were completed, then available data for the day were used. We calculated the mean and maximum daily pain for each participant at every timepoint. Subsequently, we described median of mean and maximum pain intensity scores across timepoints for every participant that submitted at least 3 days of data at each timepoint.

p Values <0.05 were considered as statistically significant, and all analyses were conducted using CRAN R v.4.0.2 and RStudio.

2.7 | Qualitative data analysis

Participant and parent interviews were transcribed verbatim. Interviews from parents were analyzed along with patient participant interviews. We used a content analysis approach that allowed for the organization of participant narratives. We developed categories a priori based on study goals, such as describing the patient experience of pain pre-HCT, the role of the pain experience in decision making regarding HCT, and pain and quality of life post-HCT. If post-HCT interviews included perspectives on any aspects of the pre-HCT experience, or experience at prior timepoints, then these were analyzed with the data at that respective prior timepoint. Coding was done by two coders and verified by a third coder for accuracy and agreement. Analyses were completed in NVivo Version 11.

The study was approved by the Institutional Review Board at Emory University, and written informed consent and assent, as applicable, was obtained prior to study procedures.

3 | RESULTS

3.1 | Participant recruitment

The study was open to new enrollment between April 2017 and November 2020. We enrolled a convenience sample of 10 participants between April 2017 and August 2019, of which eight consented for QST assessments. One patient withdrew consent following enrollment, and HCT was cancelled for one participant, so they were no longer followed on the study.

3.2 | Demographic and clinical characteristics

The median age of participants pre-HCT was 13.5 years (IQR 10.75–16.00), and two participants were female. Participants had sickle cell anemia (SCA) or similarly severe genotype. Participants had a median of two episodes of healthcare utilization for pain in the 1 year prior to HCT, and a median of 4.5 episodes in the previous 2 years. One participant had avascular necrosis of the hip. Most participants received disease modifying therapies for SCD. One participant received long-acting opioids, and two received one or more adjunctive medications for pain.

3.2.1 | HCT characteristics—Six participants (75%) received transplant from a matched sibling donor, and the others from alternative donors. All participants had successful donor-derived erythropoiesis posttransplant. Three participants experienced acute GvHD and two experienced chronic GvHD. Demographic and clinical characteristics of the study sample are reported in Table 1.

3.3 | Completion of study procedures

In Table 2, we describe the number of participants who completed study procedures and describe the number of participants who completed a given study procedure across all timepoints. For pain diaries, the number of participants who completed at least 3 days of the pain diary at each timepoint are reported. For QST assessments, if pre-HCT QST was missing, post-HCT QST was omitted. Two patients declined at least one QST assessment post-HCT. Six of the eight participants completed at least one qualitative interview.

3.4 | Pain and pain-related PROs, psychological characteristics, functional outcomes, and HRQoL

As described in Table 3, pain and PROs appeared to improve after HCT. Though the differences observed were not statistically significant, moderate to large ESs were found for most outcomes (Table S1) at 1 and/or 2 years post-HCT. We found a large improvement in physical function at 3 months post-HCT ($p = .022$, ES = .81) and a large improvement in physical function at 6 months post-HCT ($p = .052$, ES = .69) compared with baseline. There was also a trend toward significance and large improvement in pain intensity at 3 months post-HCT ($p = .059$, ES = .71). There was a trend toward significance and large improvement in sleep disturbance at 1 year post-HCT (p = 0.059, ES = .71) and peer relationships at 2 years post-HCT ($p = .056$, ES = .72). Compared with baseline, participants had an improved quality of life at 3 months ($p = .031$, ES = .88) and 6 months post-HCT ($p = .031$, ES = .88) and a trend toward significance and large decrease in total catastrophizing scores 6 months post-HCT ($p = .063$, ES = .83).

We found a heterogeneity in change in PROs and psychological factors across individuals, and across domains at 1 year and 2 years post-HCT, as shown for individual participants in Figure 1 respectively.

3.5 | Multidimensional pain diaries

The median number of diary days submitted was high overall, and median of mean pain intensity scores are reported in Table 4. There was a trend toward significance and large

decline in mean maximum daily pain intensity ($p = .059$, ES = .71) and proportion of days with pain ($p = .059$, ES = .71) between pre-HCT and 1 year post-HCT timepoint, otherwise all differences in post-HCT time points against post-HCT timepoints were not significant.

3.6 | Experimental pain sensitivity

In Table 5, we report results of experimental pain sensitivity testing. Moderate to large ESs were noted for change in PPTh (ES = .39–.58) at 1 year and 2 year post-HCT compared with pre-HCT, and a moderate ES (.39–.44) was noted for CPTh at 1 year and 2 year post-HCT compared with pre-HCT as reported in Table S2. We did not find a statistically significant change in experimental pain sensitivity post-HCT compared with pre-HCT.

3.7 | Qualitative data analysis

A total of 20 interviews were analyzed, and one interview could not be analyzed due to audio quality. The median age at enrollment of this subset was 13.5 (IQR 11–16), and four of the six were male (66.7%). We organized data largely in three major categories: (1) pre-HCT pain experience, including impact on various aspects of patient life, (2) role of the pain experience in the decision to pursue HCT, and expectations from HCT, (3) post-HCT pain experience. Although the pain experience differed between participants, most participants in this sample described a significant experience of pain pre-HCT. Pre-HCT, pain appeared to have an impact on aspects of life, particularly school, daily life activities, playing sports, and so on. Following HCT, they reported reduction or resolution of pain, improved quality of life, ability to do activities other children did or they could not do before without limitations, and some described improved energy. We also found that the experience of pain appeared to be a significant factor in their decision to pursue HCT. Categories and salient quotes are reported in Table 6.

4 | DISCUSSION

This study presents novel and unique contributions to investigating outcomes after HCT for SCD by the simultaneous use of multiple modalities of pain assessment including quantitative, qualitative, and experimental pain sensitivity methods to offer a comprehensive assessment of participant pain experience. This study highlights the heterogeneity of participant pain experience pre-HCT, and group and individual-level response post-HCT.

We have demonstrated the feasibility of collecting questionnaire and pain diary data in the context of HCT for SCD. However, this study also highlights the challenges of studying pain-related outcomes and experimental pain sensitivity in SCD, a rare disease, in the context of an uncommon, serious, and intensive procedure like HCT. As expected, there is a small sample of potential participants who may be eligible, even in very large academic centers. As potential participants for such studies are approached pre-HCT, the limited window of opportunity may coincide with the multitude of clinical assessments and procedures performed pre-HCT. In this setting, it is possible that even an observational study may pose an unacceptably high burden to potential participants. Similarly, there appears to be participant burden in obtaining post-HCT assessments, likely due to the intensive nature of post-HCT clinical care. The burden of care may be particularly high in the first year after

HCT, and likely more so among those who experience severe or significant complications related to HCT. Future studies that seek to capture pre- and post-HCT outcomes, including long-term outcomes of HCT, should consider this participant burden. In this study, flexibility in obtaining post-HCT assessments was crucial to obtaining as many post-HCT assessments as possible. Despite this, we experienced missing data. The study overlapped with the COVID-19 pandemic, during which there were substantial barriers to obtaining follow-up data. Further, due to the pandemic, the study was closed to new enrollment sooner than planned, as non-urgent transplants were deferred during this time. Last, the long duration of follow-up, while necessary to capture the change in PROs, also increases the possibility of missing data and loss-to-follow-up. This study highlights the clear need for strategies to improve remote data collection to mitigate participant burden and minimize missing data at these later timepoints.

Recurrent SCD pain episodes are a frequent indication among those who undergo HCT for SCD.[3] We did not find a statistically significant change in pain intensity or pain interference, or in mean maximum daily pain intensity as measured by a multidimensional pain dairy but did note moderate to large ES of the differences. Additionally, not all our study participants experienced high pain burden or high pain interference pre-HCT. Previous studies, however, have shown improvement in pain interference[10] and bodily pain[7] 1 year post-HCT. Although we did not find statistically significant improvements in outcomes post-HCT, pain-related outcomes appeared to be stable or improved and did not appear to be worse after HCT, as indicated by moderate to large ES of the differences in outcomes post-HCT as compared with pre-HCT. These findings were also supported by participants' reports of the impact of pain on their life pre-HCT, and perceived improvement in one or more domains of HRQoL post-HCT in qualitative interviews. It is possible that these perceived improvements coincide with increased confidence and self-efficacy that were not directly assessed in this study. The lack of statistically significant differences may be related to the small sample size, and the heterogeneity of our included sample, as not all participants experienced pain or impairment in domains of HRQoL pre-HCT. However, the moderate-large ESs of differences in outcomes indicate potential effects and should be studied with larger sample sizes. Notably, published data indicate improvement in HRQoL post-HCT,[36] particularly in physical function,[8,10] vitality,[7] and psychosocial health.[8] The role of post-HCT complications on HRQoL has not been described, but among children with SCD in a trial of HCT, there was an improvement in the change in health domain of the Child Health Questionnaire despite high rates of chronic GVHD.[9] Ongoing, large multicenter trials such as BMT CTN 1503 (NCT02766465) and BMT CTN 1507 (NCT03263559) are collecting PRO and HRQoL data in the context of HCT and will shed light on the change in these domains post-HCT. Last, we found that some individuals tend to experience substantial improvement in pain and outcomes post-HCT, though the magnitude of improvement varies across participants and across domains, suggesting there is likely both individual-level and domain-level heterogeneity in response to HCT. Hsieh et al.[5] reported a gradual reduction in hospitalizations as well as opioid use in the first-year post-HCT in adults, suggesting that change in the pain phenotype is influenced by factors other than the presence of sickle hemoglobin. The framework provided by this study may serve as a useful guide for future

similar studies examining the pre- and post-HCT predictors of improvement in pain and HRQoL after HCT.

Like the findings from the qualitative interviews in this study, previous reports indicate that relief from pain is a key consideration for individuals with SCD in the decision to pursue HCT.[4,37] Individuals with SCD who pursue HCT or gene therapy indicate that they perceive impairment in quality of life due to acute and chronic pain and seek potential curative therapies due to their debilitating pain.[38] Improved understanding of the pre-HCT pain phenotype, beyond frequency of healthcare utilization for pain, remains essential to understand more about the role of pain in decision making about HCT, particularly in those with chronic pain associated with SCD.

The experimental pain sensitivity reported here was generally comparable to previously published data in children with SCD.[13,32,39] Due to a small sample size and missing follow-up QST measurements post-HCT, we were limited in the conclusions that can be drawn. Both somatosensory deficits and pain sensitization have been described in patients who have undergone stem-cell transplantation for acute lymphoblastic leukemia.[40] Experimental pain sensitivity in SCD may also vary with age,[32] sex,[13] psychological factors,[13,41] pain frequency,[13] and may also change in response to interventions such as hydroxyurea.[39] Future studies should consider these confounding factors in studying experimental pain sensitivity in SCD in the context of HCT. Our data may also indicate the potential for pressure and cold pain sensitivity to be evaluated in future similar studies.

The strengths of this study include use of a robust multimodal framework of assessment, including medical records, PRO and psychological assessments, multidimensional electronic pain diaries, experimental pain sensitivity assessments, and in-depth qualitative interviews to provide a high-dimensional view of the pain phenotype pre- and post-HCT. The addition of qualitative interviews adds further rigor to the findings of this study. An in-depth multimodal strategy to study the pain phenotype adds to the rigor and the validity of the outcomes of a potentially curative therapy and has the potential to generate greater understanding to support patient-oriented shared decision making for HCT in SCD. The addition of qualitative research methods further complements the quantitative methods. The methods and results of this study provide a framework to conduct future similar studies with a larger sample size.

Limitations of this study include a small sample size and heterogeneity in the pre-HCT characteristics and pain burden. This may have contributed to the heterogeneity of response in pain-related PROs after HCT and a lack of statistical significance in the outcomes, possibly due to limited statistical power. Future studies should consider the heterogeneity in participant characteristics, pain burden, treatment response and the possibility of missing data and loss- to follow-up in their design, particularly with estimation of sample sizes. Future studies should also seek to identify participant characteristics associated with good pain-related outcomes post-HCT, especially amongst those who experience chronic pain.

5 | CONCLUSIONS

This study provides a framework for the conduct of multimodal pain assessments before and after HCT, which is feasible but faced with unique barriers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors thank the patients and families who participated in the study. The authors acknowledge Anarosa Campos, Ashley Griffin, Sara Moore, Toi Dickson, and Divya Veludhandi for their assistance with this study. The authors would like to acknowledge the support and contributions from Children's Healthcare of Atlanta and Emory University Pediatric Biostatistics Core. The authors thank the Mapi research trust for permission to use PedsQL™ measures. PedsQL™ contact information and permission to use: Mapi Research Trust, Lyon, France, https://eprovide.mapi-trust.org/. This study was supported by the National Heart, Lung and Blood Institute of the National Institutes of Health under award number 1K23HL140142 and 1K23HL140142-03S1 to Nitya Bakshi. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This study also received funding from the Abraham and J. Phyllis Katz Foundation by an award to Lakshmanan Krishnamurti. Soumitri Sil received funding from the National Heart, Lung and Blood Institute of the National Institutes of Health under award number K23HL133457. Asha Hurreh received support from the James T. Laney School of Graduate Studies—Summer Opportunity for Academic Research (SOAR) Program at Emory University.

Funding information

National Heart, Lung and Blood Institute of the National Institutes of Health, Grant/Award Numbers: 1K23HL140142, 1K23HL140142-03S1; Abraham and J. Phyllis Katz Foundation

DATA AVAILIBILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations:

FDI	Functional Disability Inventory
GvHD	graft-vs-host-disease
HCT	hematopoietic cell transplant
HRQoL	health-related quality of life
PCS	Pain Catastrophizing Scale
PRO	patient-reported outcome
PROMIS	Patient Reported Outcome Measurement Information System
QoL	quality of life
QST	quantitative sensory testing
SCD	sickle cell disease

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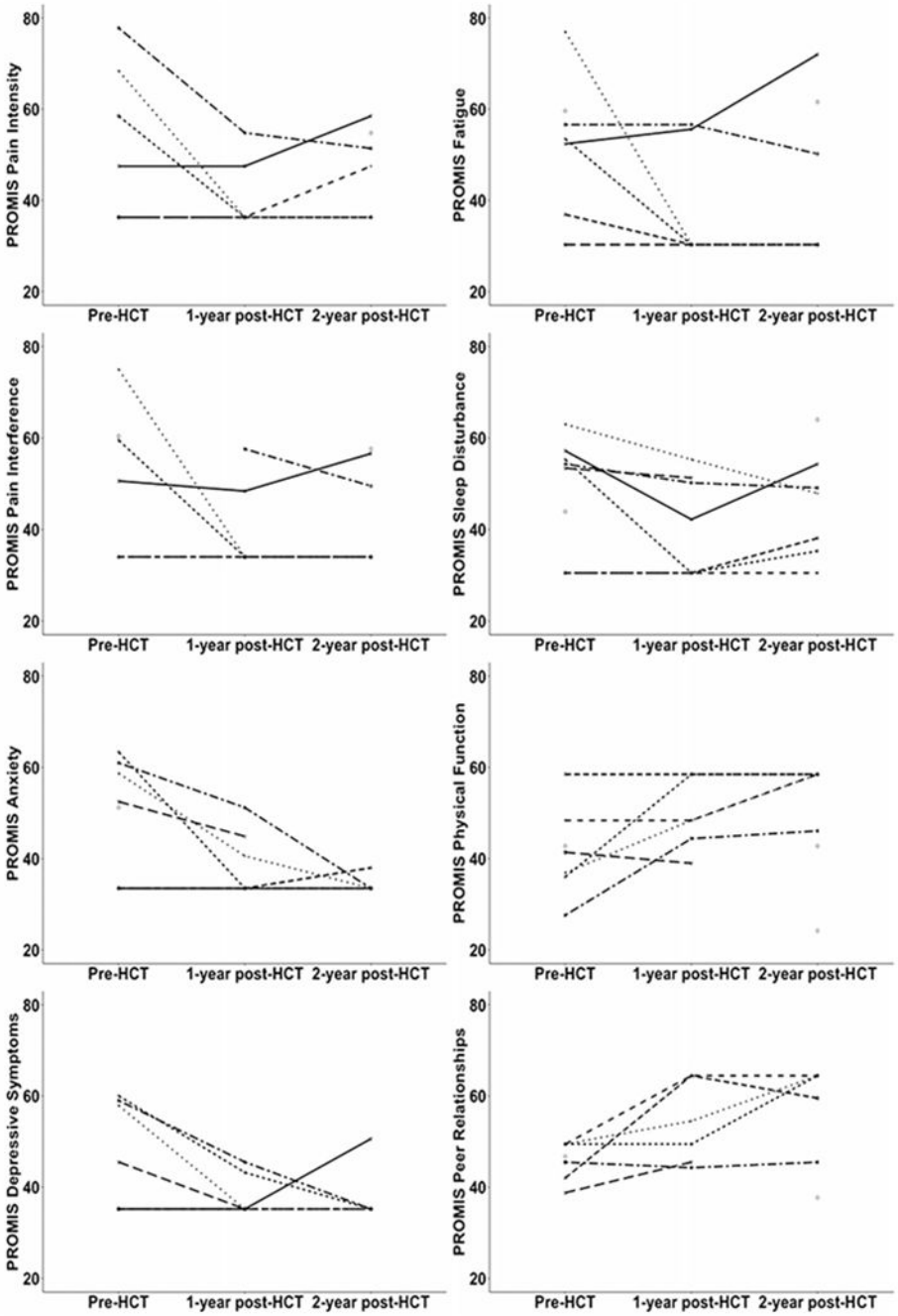

FIGURE 1.
Trends in pain and PROs following HCT for SCD

TABLE 1

Demographic and clinical characteristics

Pre-HCT clinical characteristics	
Age, median (IQR)	13.50 [10.75, 16.00]
Sex, *n* (%)	
Female	2 (25)
Male	6 (75)
SCA/SCA-like genotype, *n* (%)	8 (100)
Number of episodes of healthcare utilization for pain 1 years prior to BMT, median (IQR)	2.00 [1.00, 7.50]
Number of episodes of healthcare utilization for pain 2 years prior to BMT, median (IQR)	4.50 [3.75, 12.75]
Presence of avascular necrosis (femoral/humeral head)	1 (12.5)
Pre-HCT disease modifying therapy, *n* (%)	
Hydroxyurea	6 (75)
L-Glutamine	1 (12.5)
Chronic transfusion therapy	2 (25)
Prescribed long-acting opioids, *n* (%)	1 (12.5)
Prescribed adjunctive medications for pain, *n* (%)	2 (25)
HCT characteristics	
Type of donor, *n* (%)	
Matched sibling donor	6 (75)
Matched unrelated donor	1 (12.5)
Haploidentical donor	1 (12.5)
Presence of acute GvHD, *n* (%)	3 (37.5)
Presence of chronic GvHD, *n* (%)	2 (25)
Post-HCT donor-derived erythropoiesis, *n* (%)	8 (100)

IQR, interquartile range; Hb, hemoglobin; HCT, hematopoietic cell transplant; GvHD, graft-vs-host disease.

TABLE 2

Feasibility of completion of study procedures

	Timepoint					
Study procedures	**Pre-HCT**	**3 months post-HCT**	**6 months post-HCT**	**1 year post-HCT**	**2 years post-HCT**	**All timepoints**
Pain/outcome questionnaires, *n (One or more questionnaires per timepoint)*	8	8	8	7	7	6
Multidimensional pain diaries, *n (Minimum 3 days per timepoint)*	7	6	6	7	5	4
Experimental pain sensitivity[*], *n*	6	NA	5	4	3	3
Qualitative interviews, *n*	4	5	4[^]	4	4	1

[*] *n* = 7 consented pre-HCT. Post-HCT QST omitted if pre-HCT QST missing.

[^] One interview unable to be analyzed due to audio quality.

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TABLE 3

Patient-reported outcomes pre- and post-HCT

Measure (median [IQR], *n*)	Pre-HCT	3 months post-HCT	6 months post-HCT	1 year post-HCT	2 years post-HCT
PROMIS Pain Intensity	53.00 [36.30, 60.98], 8	36.30 [36.30, 41.90] 7$^{\wedge}$	36.30 [36.30, 51.10], 8	36.30 [36.30, 41.90], 7	47.50 [36.30, 53.10], 7
PROMIS Pain Interference	55.05 [38.15, 60.17], 6	44.10 [34.00, 58.55], 8	34.00 [34.00, 64.93], 8	34.00 [34.00, 41.20], 7	34.00 [34.00, 53.05], 7
PROMIS Pediatric Anxiety	51.85 [33.50, 59.28], 8	41.55 [33.50, 52.83], 8	33.50 [33.50, 37.92], 8	33.50 [33.50, 42.75], 7	33.50 [33.50, 33.50], 7
PROMIS Pediatric Depressive Symptoms	40.35 [35.20, 58.17], 8	37.80 [35.20, 45.98], 8	37.80 [35.20, 46.40], 8	35.20 [35.20, 39.20], 7	35.20 [35.20, 35.20], 7
PROMIS Pediatric Fatigue	52.95 [35.25, 57.35], 8	36.90 [33.60, 58.10], 7	45.35 [30.30, 59.60], 8	30.30 [30.30, 49.28], 6	30.30 [30.30, 55.90], 7
PROMIS Sleep Disturbance	53.85 [40.55, 55.77], 8	49.65 [41.48, 52.05], 8	36.35 [30.50, 55.57], 8	42.20 [30.50, 50.75], 7$^{\wedge}$	47.90 [36.70, 51.70], 7
PROMIS Physical Function	41.40 [36.67, 44.20], 8	48.00 [44.00, 53.33], 8*	53.45 [44.00, 58.50], 8$^{\wedge}$	48.40 [41.70, 53.45], 7	58.50 [44.45, 58.50], 7
PROMIS Peer Relationships	46.09 [44.60, 49.43], 8	45.47 [42.29, 46.71], 8	48.86 [30.37, 58.73], 8	51.95 [46.46, 61.95], 6	59.52 [52.50, 64.44], 7$^{\wedge}$
Pain Catastrophizing Scale	26.00 [14.00, 30.00], 5	20.50 [11.25, 30.25], 8	5.00 [2.00, 11.00], 7$^{\wedge}$	21.00 [14.00, 21.00], 5	17.50 [9.00, 25.00], 4
Functional Disability Inventory	13.04 [4.00, 19.77], 6	3.14 [1.50, 6.21], 4	7.00 [1.25, 17.25], 6	4.00 [2.00, 7.75], 4	0.00 [0.00, 2.50], 4
PedsQL Generic QoL	67.93 [50.27, 78.41], 6	85.33 [70.92, 94.84], 8*	90.76 [67.12, 94.84], 8*	90.76 [72.01, 96.47], 6	89.37 [59.51, 99.31], 6
PedsQL SCD Specific QoL	59.88 [47.38, 80.33], 7	NA	NA	NA	NA

Wilcoxon sign-rank test for matched-pairs, list-wise deletion used for unmatched pairs. All post-HCT timepoints compared with pre-HCT. Results reported without control for multiple comparisons.

$^{*}p < .05$.

$^{\wedge}0.05 > p < .1$.

Peds-QLSCD module not applicable post-HCT.

TABLE 4

Pain intensity and proportion of pain days as reported on the pain diary

	Pre-HCT	3 months post-HCT	6 months post-HCT	1 year post-HCT	2 year post-HCT	Pre-HCT/1 year post-HCT*	Pre-HCT/2 year post-HCT*
n	**7**	**6**	**6**	**7**	**5**	***p* (ES)**	***p* (ES)**
Number of diary days submitted (Median [IQR])	14.00 [10.50, 14.00]	14.00 [13.25, 14.00]	14.00 [13.25, 14.00]	14.00 [11.50, 14.00]	13.00 [13.00, 13.00]	1 (0)	.088 (.76)
Proportion of days with pain (Median [IQR])	0.21 [0.07, 0.86]	0.07 [0.02, 0.08]	0.00 [0.00, 0.00]	0.00 [0.00, 0.04]	0.00 [0.00, 0.71]	.059 (.71)	.853 (.08)
Mean of mean daily pain (Median [IQR])	0.46 [0.11, 3.71]	0.11 [0.01, 0.19]	0.00 [0.00, 0.00]	0.00 [0.00, 0.18]	0.00 [0.00, 1.36]	.093 (.63)	.583 (.24)
Mean of maximum daily pain (Median [IQR])	0.71 [0.21, 4.32]	0.21 [0.02, 0.38]	0.00 [0.00, 0.00]	0.00 [0.00, 0.21]	0.00 [0.00, 2.07]	.059 (.71)	.583 (.24)

*Wilcoxon signed-rank test, only matched pairs included ($n = 7$ for pre-HCT/1 year post-HCT and $n = 5$ for pre-HCT/2 year post-HCT).

ES (effect size) = $Z/\mathrm{sqrt}(N)$, N is number of matched pairs.

ES interpreted as small (.1), moderate (.3), and large (>.5).

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TABLE 5

Experimental pain sensitivity pre- and post-HCT

	Timepoint			
	Pre-HCT	**6 months post-HCT**	**1 year post-HCT**	**2 year post-HCT**
QST Measure (Median, IQR)	***n* = 6**	***n* = 5**	***n* = 4**	***n* = 3**
Pressure Pain Threshold, PPTh (kgf)	0.92 [0.60, 1.25]	2.01 [0.99, 2.30]	1.67 [1.49, 1.74]	1.97 [1.61, 2.30]
Pressure Pain Tolerance, PPTo (kgf)	1.6 [1.27, 2.27]	2.78 [1.75, 3.83]	2.31 [1.77, 2.98]	4.54 [4.41, 4.66]
Mechanical Pain Threshold, MPTh (g)	20.67 [9.67, 171.67]	201.33 [75.33, 300.00]	129.67 [85.08, 190.00]	77.33 [43.33, 188.67]
Cold Detection Threshold, CDT (°C)	29.76 [26.21, 30.47]	29.80 [29.75, 29.88]	27.35 [25.83, 28.95]	27.25 [27.23, 28.18]
Cold Pain Threshold, CPTh (°C)	22.05 [21.08, 24.13]	24.85 [23.00, 26.45]	16.15 [11.57, 20.92]	17.20 [15.52, 20.81]
Heat Detection Threshold, HDT (°C)	34.31 [33.53, 35.62]	34.10 [33.73, 35.15]	34.24 [34.02, 35.31]	35.58 [34.67, 35.94]
Heat Pain Threshold, HPTh (°C)	40.99 [37.50, 43.03]	39.48 [37.10, 40.12]	39.55 [35.67, 43.21]	39.88 [39.23, 40.41]
Heat Pain Tolerance, HPTo (°C)	42.99 [40.44, 44.90]	38.95 [36.38, 43.10]	40.91 [36.07, 45.40]	43.70 [42.38, 45.19]

Note: For PPTo $n = 4$ at 6 months and $n = 2$ at 2 years.

All p values were >.1.

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TABLE 6

Categories and salient quotations from qualitative interviews

Categories	Salient quotations
Impact of pain on quality of life prior to HCT For almost all participants, pain had an impact on one or more aspects of their daily life- this included school and academic activities, daily activities, sleep, physical activities done by other children their age such as sports, and other activities for fun such as playing with friends. For some, pain contributed to changes in their mood, caused stress for them and their family.	"I couldn't focus or even go to school sometimes" "Sometimes it would have me up all night, I'd get no sleep." "I couldn't play any sports." "[participant] couldn't get out of the bed, [participant] couldn't walk, [participant] didn't have an appetite, [participant] couldn't play." (Parent) "Uh a lot of hospitalization, dealing with everyday pain and not being able to live a normal life…made it very difficult to do normal activities….I would miss out on a lot of activities, the fun things" "but it did it it caused, um, a lot of change in our daily routines because of course if [participant]'s in the hospital somebody's missing work or you know it impacted the family in general" (Parent) "it made me feel like I like I'm being held back from what I could truly be" "..I just started having more pain and that's when my pain was pushing up my anxiety"
Role of pain in decision-making about HCT For most participants, pain influenced the decision to consider for HCT.	"…there was literally no end in sight. I mean, telling someone they're gonna live with that type of pain for the rest of their life is very discouraging… So definitely, just looking at the bigger picture, it was something that we wanted for [participant] and [participant] wanted for [them]self." (Parent) "I cannot go through life watching [participant] go through that like it [pain] was too much, it had got to me too much. Too much." (Parent) "..you know we was seeing when when you're a child you can't touch [participant]'s arm or move [participant] leg without [participant] screaming in pain that that played a lot into it" (Parent) "I said whatever it takes to get better" "..because I knew the transplant would potentially be my only way of being able to be normal"
Expectations from HCT Participants and/or their parent reported that they wanted to be cured of, or have no more sickle cell and/or pain.	"[Participant] leading a normal, and when I say normal doing what [participant] wants us to, not being inhibit[ed] by any type of obstacle" (Parent) "No more sickle cell" "I'll be cured… … …. No more pain" "to be able to go to school and be able to just enjoy my life"
Pain experience post-HCT Most participants did not report sickle cell pain post-HCT. Participants reported that they enjoyed participating in activities other children did, and not having the limitations they had before. Some participants indicated they felt less tired and had more energy. Some participants described the challenges they had transplant related restrictions, particularly early post-HCT.	"being active again just knowing that I get to do stuff that I couldn't do before" "[participant] plays all day long [participant] can go outside without getting sick and having you know getting tired and have to sit down constantly.."(Parent) "I was able to do things that I wanted to do" "[participant] has no feeling of say oh I'm tired or um, ok I maybe won't do as much [participant] doesn't do that [participant] just goes for everything."(Parent) "But I know that's like eighteen years catching up but I know I can like at least run and all that" "have been able to do more things and spend time with people and not have to worry about doing activities that could potentially send me into a pain crisis"

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