Understanding patterns and correlates of daily pain using the Sickle cell disease Mobile Application to Record Symptoms via Technology (SMART)

Patients with sickle cell disease (SCD) manage most pain symptoms or events at home without seeking medical help (Smith *et al*, 2008). Thus, to have the largest impact on patients' functioning and quality of life, we should focus more on assessment and treatment of daily pain rather than episodic acute pain that requires emergent care (Amr *et al*, 2011). We need innovative approaches to better understand daily pain patterns and factors associated with changes in pain intensity and frequency. In the current study, we use a mobile e-diary app to describe day-to-day patterns in SCD-related pain symptoms and identify the clinical and demographic factors associated with differences in daily pain level among adult patients with SCD.

Three sickle cell centres, located in large urban medical centres, used the sickle cell Mobile Application to Record symptoms via Technology (SMART) for ongoing studies. This study combines data from two independent clinical trials with similar daily pain tracking protocols (NCT01833702, NCT02384590). The trial conducted at University of Pittsburgh (Pitt) and Vanderbilt University (Vanderbilt) asked participants to use SMART for at least 6 months, while the clinical study at Duke University (Duke) asked participants to use the app for at least 1 month. Eligible participants were all aged ≥18 years with a confirmed diagnosis of SCD.

For all participants, SMART was installed either on the patient's own iOS mobile device (iPad or iPhone) or one we provided, to track daily pain. Pain was recorded on a 0-10 visual analogue scale (VAS), with location of pain as a drop-down list. For each participant, a list of pharmacological interventions used was generated from current medications listed in medical records. Participants received push-notification reminders to record symptoms twice a day. Additional details on SMART are available (Shah *et al*, 2014; Jonassaint *et al*, 2015).

T-tests and analyses of variance (ANOVAs) were used to compare the mean of the within-patient averaged pain levels. To account for within-patient correlation in the VAS pain reports, we fitted several linear mixed models, including both fixed effects for the independent variables and random effects at the patient and institution level. Multivariate models included as covariates: institution, gender, age, hydroxycarbamide use, folic acid use, long- and short-acting opioid use, and non-opioid pain medications. Time of day was assessed as a categorical variable.

Table I. Demographic and clinic characteristics of the study sample.

Variable	N	%
Female	23	59·0
Age (years)		
18–34	24	61·5
≥35	15	38·5
Use of hydroxycarbamide	27	69·2
Use of Folic acid vitamin	26	66·7
Ever long-acting medication user	29	74·4
Ever short-acting medication user	35	89·7
Ever non-opioid medication user	29	74·4
Sickle cell disease genotype		
HbSC	8	20·5
HbSS	20	51·3
$S\beta^{+}$Thal	5	12·8
$S\beta^{0}$Thal	3	7·7
SO^{arab}	3	7·7
Total number of final sample (patients)	39	

The sample included 47 patients (mean age 33 ± 11·6 years) from Duke (n = 19), Vanderbilt (n = 8) and Pitt (n = 20). Eight participants were excluded from analysis due to having ≤5 entries (n = 6) or because VAS pain reports never exceeded 0 (n = 2). As presented in Table I, the final analysed sample included 39 participants with various types of SCD, including type SS, SOarab, SC, $S\beta^{+}$ and $S\beta^{0}$ (n = 3, 7%). Most participants were prescribed hydroxycarbamide (69%) and folic acid (66%). In addition, the majority were treated with pain medications including long-acting narcotics (74%), short-acting narcotics (88%) and non-opioids (74%). The 8 excluded participants were younger, and less likely to be taking folic acid or short-acting opioids.

Participants used the SMART app for 164·6 ± 109·6 days, with a mean of 67·2 ± 60·4 pain reports per participant. The most frequent reporting occurred between 18 and 24 h (n = 911) and the least frequent between 0 and 7 h (n = 221). Mean of pain scores over the total study period was 4·7 ± 2·1 (range 0–10). The median use of SMART was similar at each institution and there were no use differences by demographic or clinical factors. A rapid decline in reporting occurred between Week 1, with 7·38 mean reports, and Week 6, with 3·72 mean reports (Figure S1). Reporting

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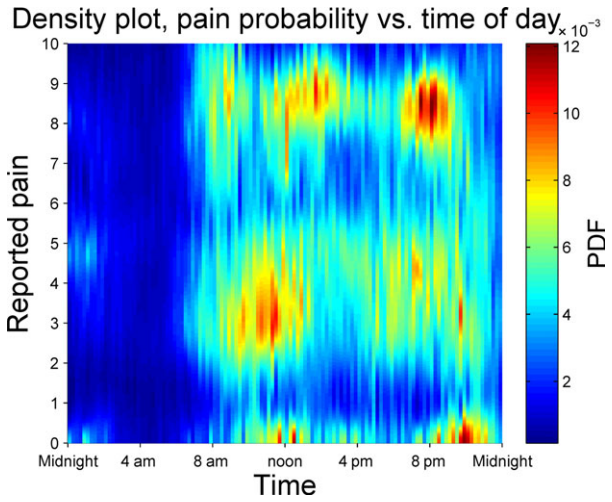

Fig 1. Probability density function (PDF) plot of pain probability versus time of day for adults with sickle cell disease.

stayed relatively stable thereafter, not falling below an average of 3·0 reports until week 19. Although most participants decreased frequency of reporting over the course of the study, seven did not show a decrease until their last report.

Linear mixed models showed genotype SC was associated with significantly lower mean VAS pain levels than either of the most severe genotypes SS or $S\beta^0$ ($b = 2{\cdot}15$; $P = 0{\cdot}04$). Using folic acid (regression coefficient (b) $= -0{\cdot}39$; $P = 0{\cdot}04$) and non-opioid pain medications ($b = -2{\cdot}06$; $P = 0{\cdot}006$) was also significantly associated with lower VAS pain level compared to not using those medications. There was a statistical trend toward use of short-acting opioids being associated with higher VAS pain level ($b = 1{\cdot}33$; $P = 0{\cdot}09$). There was no effect on VAS pain with regard to age, gender, hydroxycarbamide, long-acting opioids or institution differences. After controlling for the effect of other covariates, using folic acid ($b = -0{\cdot}41$, $P = 0{\cdot}03$) and non-opioids ($b = -2{\cdot}25$, $P = 0{\cdot}004$) was still significantly associated with lower VAS pain levels.

Density plot of pain probability vs. time of day found a cluster of highest pain reports between 8 pm and 9 pm (Fig 1). Highest probability of recording was found between 11 am and noon, with both higher and lower pain scores recorded frequently during this time.

On average, patients reported pain using an electronic pain diary app for about 6 months and entered data every 2–3 days. Several trends or significant associations in the expected direction help support the validity and accuracy of this data capture method. For instance, patients reported spikes in pain at night and those taking non-opioid pain medications had 2·3/10 points lower average pain on the VAS, while those prescribed a short-acting opioid for pain had 1·3/10 points higher average pain.

Like other remote symptom-reporting tools (Whitehead & Seaton, 2016), app use was more frequent at the beginning of the reporting period and then decreased over time. Further, there were significant individual differences in the frequency of reporting, with several individuals reporting fewer than five times and others reporting nearly every day. Future studies of SMART would benefit from strategies to increase engagement. We note, for example, that participants received no compensation or incentives for their daily reporting in any of these studies, thus there were no external incentives for engagement.

Despite a limited sample size, this study provides strong evidence supporting the use of mobile technology for measuring daily pain and symptoms in SCD. Ecological momentary assessment may be an effective and accurate means for evaluating treatment outcomes and pain trajectories in this population. Future studies using this methodological approach will help identify patient-specific differences in pain patterns and ultimately build prediction models for changes in SCD-related symptoms.

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Author contributions

All authors have contributed substantially to the research design, or the acquisition, analysis or interpretation of data; drafting the paper or revising it critically; and approve of the submitted and final version of this manuscript.

CRJ, JCJ, LD, MS and NS performed the research. CRJ, JCJ, LD, DMA, CK, JJL and NS designed the research study. CK, DMA, JJL, JM, YJ and QI analysed and interpreted the data. CJ, CK and NM wrote the paper.

Disclosures

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Conflict of Interest: Jude Jonassaint is owner of SickleSoft, Inc., the IT company responsible for early development of SMART. SickleSoft does not own rights or patents associated with SMART.

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Supporting Information

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

Fig S1. Patient-specific line plots (Spaghetti plot) of the total number of reports per patient by week and a mean curve across all patients (thick red line).

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