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Understanding Patterns and Correlates of Daily Pain using the Sickle Cell Disease Mobile Application to Record Symptoms via Technology (SMART)

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Keywords

Health information technology; mobile app; pain; patient reported outcomes; sickle cell disease

Patients with sickle cell disease (SCD) manage most pain symptoms or events they experience at home without seeking medical help (Smith et al., 2008). Thus, to have the largest impact on patients' functioning and quality of life, there should be more focus on assessment and treatment of daily pain rather than episodic acute pain that requires emergent care (Amr, Amin, & Al-Omair, 2011). To accomplish this, we need a better understanding of daily pain patterns and factors influencing changes in pain level day-to-day, which currently pose a challenge for medical management (Smith et al., 2008). There is limited information, however, on the daily variability of pain and what factors are associated with increases in SCD pain frequency or intensity. Innovative techniques are critically needed to better understand, describe, and allow better pain treatment. In the current study, we aim to use a mobile e-diary app to describe day-to-day patterns in SCD-related pain symptoms and

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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.

identify the clinical and demographic factors associated with differences in daily pain level among adult patients with SCD.

METHODS

Three sickle cell centers located in large urban medical centers utilized 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 (ClinicalTrials.gov NCT01833702, NCT02384590). The clinical trial conducted at University of Pittsburgh (Pitt) and Vanderbilt University (Vanderbilt) asked participants to use SMART for at least 6 months, and the clinical study at Duke University (Duke) asked participants to use the app for at least 1 month. Eligible participants were all >18yo with a confirmed diagnosis of SCD.

All participants were given SMART installed on an iOS mobile device (iPad or iPhone), either their own or one that we provided, to track their daily pain and interventions used. Pain was recorded on a visual analog scale (VAS) with location of pain as a drop-down list. The list of pharmacological interventions taken was customized for each patient and generated from the patient's current medications listed in medical records. Participants received push-notification reminders to record symptoms twice a day. Additional details regarding SMART have been described in previous reports (Shah, Hemoglobin 2014; Jonassaint, Hemoglobin 2014). Participants received no payment for their entries.

Analysis.

We categorized five sickle-cell genotype groups: type HgbSS, HgbSC, $S\beta^+$, $S\beta^0$ and SO^{arab}. T-tests and ANOVAs compared 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 institutions level. We modeled a compound symmetric correlation matrix for within-patient pain reports. The multivariate models included as covariates institution, gender, age, hydroxyurea use, folic acid use, long-acting and short-acting opioid use, and non-opioid pain medications. Time of day was assessed as a categorical variable.

RESULTS

The sample includes 47 patients (mean age 33 years old ± 11.6) from the three institutions: Duke (n = 19), Vanderbilt (n = 9), and Pitt (n = 20). Eight participants were excluded from analysis due to having ≤ 5 entries (n=6) or VAS pain reports never exceeded 0 (n=2). The final analyzed sample included 39 participants with varying types of SCD including type SS/SO-Ara (n=23, 60%), SC (n=8, 21%), $S\beta^+$ (n=5, 13%), and $S\beta^0$ (n=3, 7%). Most participants were prescribed HU (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 FA vitamin 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 18–24 hrs (n=911) and the least frequent between 0–7 hrs (n=221). Mean pain scores over the total study period was 4.7 ± 2.1, as measured by the electronic VAS. 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 from week 1 with 7.38 mean reports to week 6 with 3.72 mean reports. Reporting stayed relatively stable thereafter not falling below 3.0 reports on average until week 19. Although most participants decreased their frequency of reporting over the course of the study, n=7 did not show such decreasing pattern until their last report.

Medications, clinical factors and pain level.

The linear mixed models showed sickle cell genotype SC was associated with significantly lower mean VAS pain levels than either of the most severe genotypes SS or Sβ0 Thal (b=2.15; p=.0.04). Using folic acid (regression coefficient (b)=−.39; p=.04) and non-opioid pain medications (b=−2.06; p=.006) was also significantly associated with lower VAS pain level as compared to those who reported not using those medications. There was a statistical trend toward the use of short-acting opiates being associated with higher VAS pain level (b=1.33; p=.09). There was no effect on VAS pain for age, gender, HU, long-acting opioids, or institution differences. After controlling for the effect of other covariates (SCD diagnosis, age, gender, HU, folic acid, long-acting narcotics, short-acting narcotics, and non-opioids), using folic acid (b=−0.41, p=0.03) and non-opioids (b=−2.25, p=0.004) was still significantly associated with lower VAS pain levels.

Time of day differences.

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

Discussion

On average, patients reported pain using an electronic pain diary app for about 6 months and entered data every 2 to 3 days. There were several trends or significant association in the expected direction, which helps support the validity of this data capture method. For instance, patients 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. Thus, patients were likely fairly accurate in their report of pain using the electronic VAS.

Like other remote pain reporting tools, app use was more frequent at the beginning of the reporting period and then decreased over time (Becker et al., 2015; Runyan et al., 2013; Whitehead & Seaton, 2016). 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. As attrition and non-adherence are typical for electronic health interventions and remote monitoring tools, future studies of SMART would benefit from

implementation of strategies to increase engagement. We also note that participants received no compensation for their 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. These data suggest that ecological momentary assessment may be an effective and accurate means for evaluating treatment outcomes and pain trajectories in this population.

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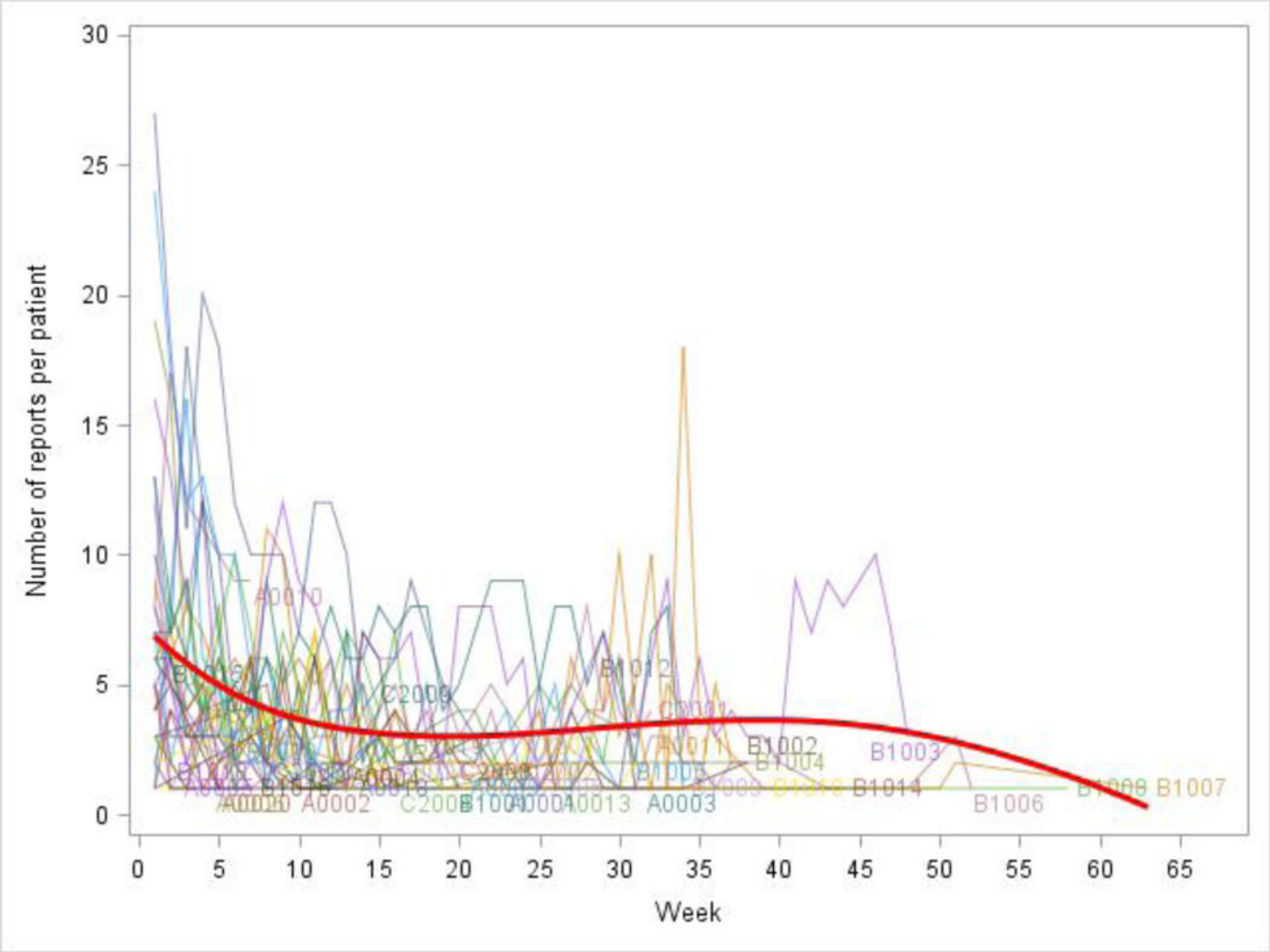
Appendix



Appendix Figure 1.

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

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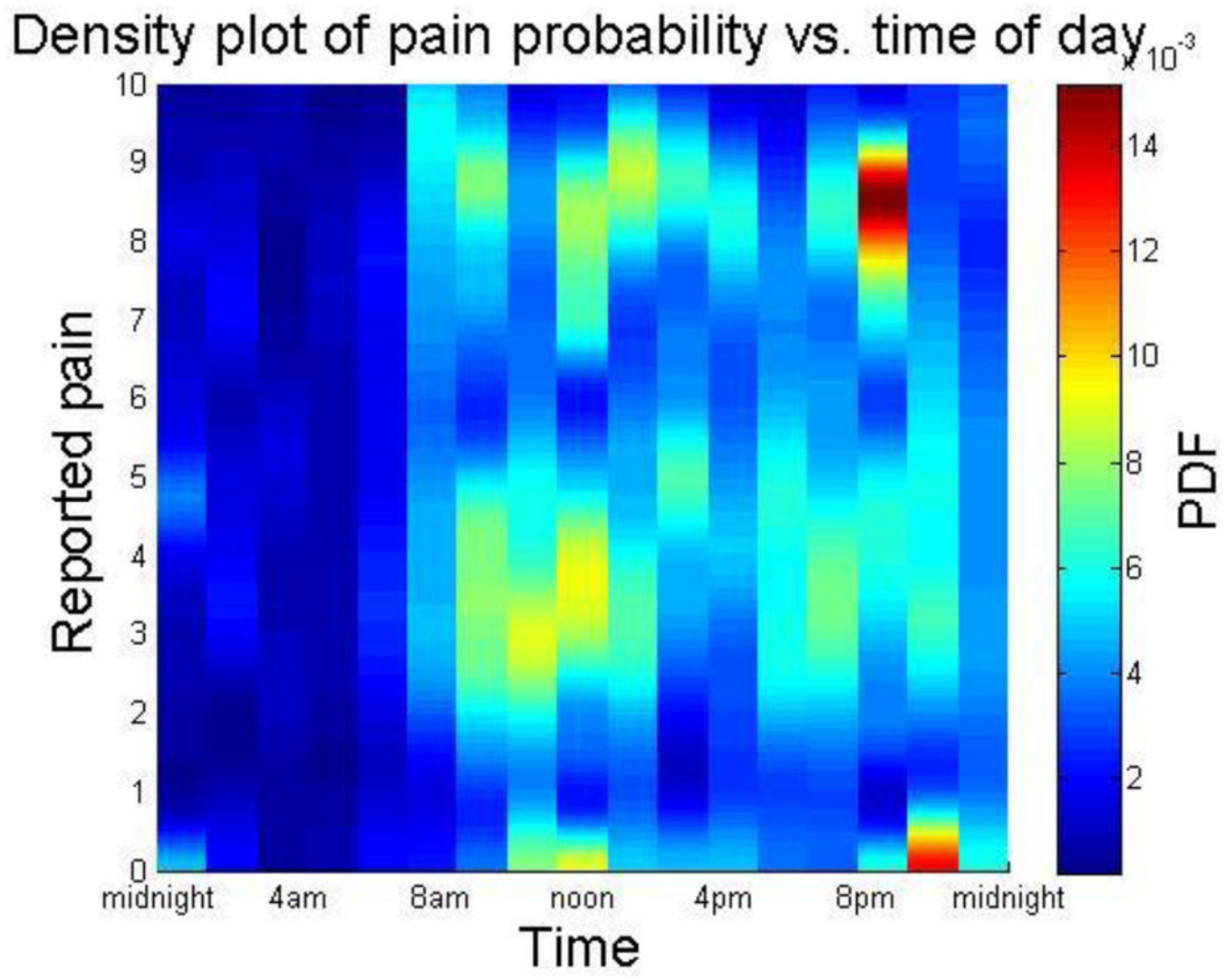

Figure 1.

Table 1.

Demographic and clinic characteristics of the study sample

Variable	value	N	Percent
Female		23	59.0
Age	18–34 yrs	24	61.5
	>=35 yrs	15	38.5
Use Hydroxyurea (HU)		27	69.2
Use 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
SCD disease type	HgbSC	8	20.5
	HgbSS/SO-Ara	23	59.0
	Sβ+Thal	5	12.8
	Sβ0Thal	3	7.7
		39	
Total number of study sample (patients)			