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Pain Site Frequency and Location in Sickle Cell Disease: the PiSCES Project

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Abstract

Treatment options for sickle cell disease (SCD) pain could be tailored to pain locations. But few epidemiologic descriptions of SCD pain location exist; these are based on few subjects over short time periods. We examined whether SCD pain locations vary by disease genotype, gender, age, frequency of pain, depression, pain crisis or healthcare utilization.

We enrolled 308 adults with SCD in 2002–2004. Subjects kept daily pain diaries for up to 6 months, including a body chart. Analyses employed mixed model and generalized estimating equations.

260 subjects completed at least one body chart. An average of 3.3/16 sites (25%) were painful. The number of pain sites varied by age, depression, frequent pain days, crisis and unplanned hospital/ED utilization. Lower back, knee/shin and hip, hurt on average more than a third of pain days, while jaw and pelvis hurt on fewer than 10% of days. Odds of a crisis were increased substantially when pain was in the arm, shoulder, upper back, sternum, clavicle, chest or pelvis (OR>1.5) while the odds of unplanned utilization were substantially increased for the sternum, clavicle and chest (OR>2.0).

Pain in SCD varies considerably both within and between subjects, although it occurs most commonly in the lower back and lower extremities. The number and location of pain sites varies significantly by age, frequent pain, crisis and utilization. Identification and understanding of combinations of pain location and intensity may help to understand the etiology of SCD and improve SCD management.

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Introduction

The majority of medical contacts in sickle cell disease (SCD) are for exacerbations of pain due to vaso-occlusive episodes, commonly called “crises” [21]. Vaso-occlusive pain in SCD is classically described as occurring in the back, chest, and extremities. This clinical observation is supported by limited empirical evidence [4,7–11,20,21,32].

However, vaso-occlusive pain of the trunk and extremities is not the only kind of pain people with SCD experience. Severe, sometimes prolonged pain may also come from priapism [15, 25,33], avascular necrosis of the hip, shoulder, or knee[22], or venous stasis ulcers of the ankle and leg [32]. Chest pain can result from acute chest syndrome, a cascade that can result from any one of several inciting events, most notably viral and bacterial pneumonia, fat embolism, and in situ sickling in the lung [34,35]. Acute abdominal pain may result from cholecystitis due to the almost ubiquitous bilirubin-containing gallstones from chronic hemolysis, appendicitis, or from an “abdominal crisis”, which may represent bowel ischemia [32]. Headache may herald impending or actual subarachnoid hemorrhage. Since pain location may vary for each of these sickle-cell related complications or manifestations, appropriate treatment for SCD pain could vary widely.

Pain location could well be indicative of the etiology of the pain syndrome. One reason to explore pain location in SCD is to determine whether pain location resembles that of other chronic painful diseases for which more is known about the mechanisms of pain (e.g, diabetic neuropathy, Raynaud’s phenomenon, rheumatoid arthritis, and peripheral vascular disease).

For example, several [17,23] have proposed cooling as predictive of pain location in SCD. The “steal syndrome” hypothesis [27], supported by anecdotal evidence in Jamaicans and others [1,2,18,24,26], predicts that exposure to cold causes constriction of superficial blood vessels in the skin and muscles and shunts blood inward. In SCD patients, such shunting would take blood away from the bone marrow of distal bones, producing pain in those body sites.

Thus, several questions about pain location arise for physicians managing SCD patients, especially when prescribing empiric, high-dose opioids to sometimes unfamiliar patients. How true is the classic picture of the most common sites for vaso-occlusive pain? How do the number and location of pain sites vary among patients? Are the number or location of sites associated with overall pain intensity, and thus the need for more or less analgesia? Does severity of sickle cell disease, as represented by genotype, comorbid conditions, crises, unscheduled health care utilization, and frequency of pain, influence number of sites or pain location? Do characteristics often associated with pain such as age, gender and depression influence pain locations?

Few detailed descriptions of SCD pain exist to answer these questions. Therefore, as part of a large cohort study of the epidemiology of daily pain in SCD, we examined subjects’ reported number of pain sites, and whether pain locations vary by age, genotype, gender, coexisting depression, frequency of pain, presence of subjective crisis, or by likelihood of hospital or emergency department utilization.

Methods

Study description

The Pain in Sickle Cell Epidemology Study (PiSCES) is a longitudinal cohort study of adult subjects with SCD designed to understand the relationship between pain and response to pain. The emphasis is on potentially mutable etiologic, and non-biologic variables. The PiSCES methods have been described in detail elsewhere [28]. Briefly, 308 adult subjects with SCD were enrolled in the PiSCES project from July 2002 through August 2004. Baseline data was

collected at the time of enrollment using a self-administered questionnaire which included questions on demographics, health related quality of life, depression (using the Patient Health Questionnaire[30]) and other information including self-reported comorbid conditions. Blood was obtained for genotyping. Subjects were also asked to complete daily diaries.

Sample

Subjects with SCD aged 16 or older were recruited statewide through a variety of networks including established clinics, health fairs, referrals, and targeted mailings. Subjects were recruited from specialty centers (i.e. centers with well structured sickle cell management programs) as well as community centers. The majority of the subjects came from the Richmond and Tidewater areas, as these areas have the highest population of African-Americans. The study was approved by the Institutional Review Board of Virginia Commonwealth University. Informed consent was obtained on all subjects.

Pediatric patients less than 16 years of age were excluded, because they may differ substantially from adults in both their clinical course and healthcare utilization patterns. Patients on chronic exchange transfusion were excluded because of effects on hematologic factors and pain. Patients too cognitively impaired (mini-mental status score <27), or otherwise unable to complete diaries were excluded. Of an estimated 1,000 SCD patients in the state of Virginia, over 300 eligible participants were recruited.

For the current analyses, we included all PiSCES subjects who submitted at least one diary indicating pain. Twenty three subjects who never submitted any diaries, plus an additional 25 subjects who did not report any pain on their diaries were thus excluded, leaving 260 subjects with a total of 15991 diaries/body charts for analysis.

Diary—Immediately after enrollment and completion of the baseline survey, subjects began daily diary completion. Subjects were asked to fill out daily diaries for 6 months. The diary was modeled after the one used in the Multicenter Study of Hydroxyurea [6]. Every month, subjects were compensated based on the number of diaries completed and returned, with increasing compensation over the course of the study to encourage continued participation. Among other things, the diary asked subjects to report about the previous 24 hours: the worst sickle cell pain intensity, on a scale from 0 (none) to 9 (unbearable), whether or not they were in a sickle cell crisis, and whether they had gone for an unscheduled physician visit, emergency department (ED) visit or were hospitalized due to sickle cell pain.

Subjects were also asked to mark a body chart, indicating where they hurt. Both front and back views were included on the diary. Subjects were specifically asked to “place an “X” in each box where, due to sickle cell pain, you hurt yesterday”. There were 128 possible boxes that could be marked each day. The body chart did not name body sites. Body sites were later defined by aggregating boxes defined a priori by physician investigators experienced in treating sickle cell patients [WRS, JDR]. Subsequently, a cluster analysis. which statistically aggregated the boxes was run for validation purposes (using PROC VARCLUS in SAS version 9.0 [SAS Institute, Cary NC]). The clusters formed agreed with those defined a priori, thus validating the choice of clusters. Sixteen different sites were thus defined: head, jaw, shoulder, clavicle, sternum, chest, abdomen, arm, hand, hip, thigh, knee/shin, ankle/foot, pelvis, upper back and lower back. These sites were also classified as proximal or distal, where ankle/foot, knee/shin, thigh, hand and arm were defined as distal body sites and the rest were considered proximal. *Number of body sites* was defined as the total number of body sites (of 16) that hurt for a given study participant on a given day.

Statistical Methods—In order to assess within and between subject variation in pain sites, we calculated the percent of pain days each subject hurt at each body site, and examined the

distribution across subjects. Mixed model analysis of variance was used to estimate the mean number of body sites on the body chart that hurt, as well as differences by gender, sickle cell genotype (SS or β° vs SC or β+ thalasemia), depression (Y/N), frequent reporting of pain (defined as reporting pain on at least 67% of submitted diaries-the median), crisis(self-reported Y/N) and healthcare utilization(self reported use of emergency room, overnight hospitalization or unscheduled clinic visit) on these measures. In order to determine if number of diaries submitted by subjects was a confounder for these relationships, mixed model regression was also performed, with outcome measure the pain intensity or number of painful body sites, and number of submitted diaries as the predictor. Generalized estimating equations (GEE) with a logit link were used to estimate the frequency of pain at each body site, as well as to determine the multivariate relationship of age, gender, genotype, depression and pain frequency with reporting of pain at each of 16 specific body sites. Similar analysis was used to determine which body sites were predictive of crisis or utilization, controlling for covariates. Because pain frequency (percent days with pain) was found to not satisfy linearity assumptions, the variable was dichotomized at the median of 67% of days. Both approaches (mixed models and GEE) accounted for nesting of diary days within subject. Correlation between number of pain sites marked with pain intensity was calculated for each subject, and then averaged using Fisher's z transformation.

Results

Table 1 describes the PiSCES analysis sample (n=260). Subjects were between 16 and 64, with mean age 33.9. Approximately 60% were female, 62% never married, 50% graduated had some college education, and 71% were of SS genotype. Forty percent had household income less than $10,000 income, while 21% had over $30,000. Thirty percent were depressed at baseline. Subjects who were excluded from analysis (n=48) were marginally less likely to be depressed (16.7% vs 30.4%, p=0.0524) and were younger (29.5 yrs vs 33.9 yrs, p=0.012); otherwise the analysis sample did not differ on gender, genotype, education, income or marital status (all $p \geq 0.13$).

Table 2 shows pain intensity and number of body sites marked on pain days. Overall, mean pain intensity was 4.50 with an average 3.3 of 16 body sites marked as painful. Mean pain did not differ by gender, age or genotype, but subjects with comorbid depression and those with more frequent pain had higher pain intensity, and pain intensity was higher on days with crisis or utilization. More pain sites were reported by subjects who were depressed as compared to those who were not (3.8 vs 3.1, p=0.0011), and those 45 years and older as compared to younger subjects (2.7 vs 3.3 vs 4.0, p=0.0120 for overall test, p=0.049, 0.0030 respectively, Tukey adjusted pairwise comparison). More pain locations were also reported on days when subjects reported being in crisis vs non-crisis days (4.2 vs 3.1, $p<0.0001$), or when they utilized unplanned medical services (4.5 vs 3.6, $p<0.001$). Number of pain sites was only moderately correlated with pain intensity ($r=0.391$, $p=<0.0001$). Number of diaries submitted by subjects was not significantly related to either pain intensity or number of pain sites, indicating that number of diaries was not a confounder in any of these relationships.

In order to assess within and between subject variation in pain sites, we examined the distribution of the percent of pain days each subject hurt at each body site. Some subjects never reported sickle cell pain at certain locations, while some subjects reported pain at the same site virtually every day. More commonly, subjects reported at least some pain occasionally at each site. The mean percent of pain days that a subject reported pain at a site ranged from 5% to 42%, indicating that there was day – to – day variation within subject as to painful body sites. The average percent of days that subjects hurt at any site also varied from subject to subject (standard deviation between subjects ranging from a low of 13.7 for the jaw to 36.0 for the lower back).

The most common pain sites were lower back, knee/shin and hip, which hurt an average of more than one third of pain days. Least painful were jaw and pelvis, with pain at these sites on fewer than 10% of days (Figure 1). Pain in distal sites did not occur more often in cold weather months (November –February) than others (72.6 vs 72.8% of days, p=0.9048); pain in the legs and feet occurred 57.3% of days as compared to pain in the hands or arms (32.6% of days).

Table 3 shows the multivariate relationship between age, gender, genotype, depression and pain frequency, with pain at each body site. Frequent pain was associated with increased odds of pain in the head, shoulder, lower back, arm, hand, ankle/foot, knee/shin, thigh and hip. Increasing age was significantly associated with pain in the ankle/foot, shoulder, clavicle, hand and arm. Males had significantly lower odds of thigh pain but increased odds of pelvic pain. Subjects with SC genotype were at significantly increased odds of thigh pain, while depressed subjects had higher odds of head pain. For other body sites (upper back, abdomen, chest, sternum and jaw), location did not vary by age, sex, genotype, pain frequency or depression.

There were significantly increased odds of a subject reporting crisis associated with pain at each body site. Seven of the sites (arm, shoulder, upperback, sternum, clavicle, chest and pelvis) had at least a 50% increase in odds of crisis, compared to noncrisis pain days The relative odds that a subject sought unplanned medical attention for sickle cell pain was increased when pain was in the lower back, knee/shin, hip, thigh, arm, shoulder, upper back, sternum, clavicle and chest. Relative odds of utilization were more than double when pain occurred in the sternum, clavicle and chest as compared to no pain at these sites (Table 4).

Subjects with a history of aseptic necrosis (n=54) had higher relative odds of hip pain (OR=3.13, 95% CI: 2.09, 4.72) but not shoulder pain. Men reporting a history of priapism (n=15) did not report more pelvic pain (p=0.4401), nor did subjects reporting history of ischemic ankle ulcers (n=31) report ankle/foot pain more often (p=0.1041) or those with gallstones (n=138) report abdominal pain more often (p=0.1066), compared to those not reporting such pain.

Discussion

We report here results of the largest study to date using daily diaries to describe the number and location of pain sites in adults with SCD. Our results confirm some previous studies' reportedly high frequency SCD pain sites as those most often painful in SCD[7–11,21,32]. Our results extend some of the conclusions about the number and location of pain sites in SCD reached in previous studies, to a large number of subjects studied up to six months. Our results also provide new detail and new conclusions about pain sites in SCD adults.

We found that when pain occurred in people with SCD, it affected on average about 3 (21%) of the 16 pain site categories we defined. The locations of pain varied between individuals, and from day to day within individuals. We identified the lower back and knee/shin as the most frequent SCD pain sites, but found that on average, no one body site was identified as painful for more than half of all subject pain days reported. Some sites, including the pelvis and jaw, were, on average, painful for less than 10% of patient pain days.

Contrary to expectations, we found that subjects with SS genotype, commonly felt to be the more severe genotype, did not report pain at more sites than those with the SC genotype, nor was the average intensity of their pain higher. It is not clear whether this is due to survivor bias (SS subjects living well into adulthood having less severe disease than younger people with SS) or there is some other underlying reason for this result. While SS subjects in our sample tended to be slightly younger (33.1 years vs 36 years, p=0.0685), controlling for age did not change the relationship.

We found that the number of body areas that were painful was not significantly higher in women, which is consistent with what we have reported previously regarding lack of gender differences [16]. The increased odds of pain in the pelvic area for males is consistent with priapism, yet men reporting a history of priapism at baseline were no more likely than those not reporting such to indicate pelvic pain on their diaries. We also found that people with SCD who were depressed at study entry reported somewhat more intense pain, and more pain sites than those without, again consistent with our own report from this SCD cohort which studied depression and pain intensity[13] as well as other studies of depression and non-SCD pain [12,19]. Our finding that subjects with comorbid depression had head pain more often than non depressed subjects, an unusual location in SCD, should be explored further in other SCD populations to determine if it is reproducible. If so, it may be of important diagnostic significance in SCD patients with otherwise undiagnosed depression.

As expected, we found more intense pain and a greater number of painful sites on days subjects reported they were experiencing a crisis compared to non-crisis days. We found similar differences on days patients reported health care utilization vs none as well. Of particular interest is that subjects with pain in the sternum, clavicle or chest had more than twice the odds of seeking medical treatment for their SCD pain than those without. These are sites that are not often reported as sources of sickle cell pain (10%–12%), so their occurrence may cause concern and prompt action such as seeking medical care. Whether these pain sites are associated more often with serious SCD complications remains to be demonstrated, but it is possible that pain location may be useful in identifying conditions that require immediate medical attention.

We did not find pain more often in distal pain locations in cold months as compared to other months. Thus our findings do not support the “steal syndrome” hypothesis[27]. Our results that pain in the legs and feet occurred more often than in the hand and arm suggests that mechanism of pain in SCD may be more similar to diabetes and peripheral vascular disease, as opposed to Raynauds disease or rheumatoid arthritis.

We found few descriptions of SCD pain location and frequency with which to compare our results. The studies that we found tended to focus on children, and were mostly conducted among inpatients; they also tended to be either based on relatively few subjects or were conducted over short time periods (often a single day).[7–10,14–15,31] Most found that reported pain in children predominated in the chest and abdomen. While this is in contrast to results in our adult population, where pain at these sites was relatively rare, our subjects were reporting more often on days without crisis or hospital utilization. In fact, pain in the chest was an indicator of a higher likelihood of hospital utilization in our subjects. [5,9–11,14] Although the few studies that reported on adults only included subjects in crisis[3,26], they tended to report more back and leg pain than with children, in agreement with our findings.

There are several limitations to this study. The study was conducted in a single site and thus generalization may be limited, although there is no reason to believe that SCD pain is experienced differently in other parts of the US. Subjects were only asked to mark location of pain, but not the corresponding intensity, so we could not directly link varying intensity to specific body sites. While the subjects were instructed to only indicate pain associated with sickle cell disease, the ability of subjects to distinguish sickle cell from other pain is not known. Subjects submitted varying number of diaries out of the maximum possible 188 and it is possible that this could have influenced results. But statistical analysis adjusted appropriately for multiple measures per subject and specific analysis showed that number of submitted diaries was not a confounder of pain intensity nor number of pain sites. Finally, the study was epidemiologic, and not etiologic. Thus the results raise hypotheses to be pursued by future studies as opposed to definitively answering questions.

In our previous work, we demonstrated that pain frequency and intensity in SCD were far more complex than their original simplistic definitions relying on pain associated with healthcare utilization [29]. The current findings further suggest that there is substantial variation, both within and between people with SCD, in the locations of SCD pain, and that some of this variation is associated with patient characteristics. It remains to be seen whether this variation in pain location is associated with longer-term clinical outcomes or prognosis, and ongoing work should focus on whether identification and understanding of combinations of pain location and intensity offer improvements in SCD management.

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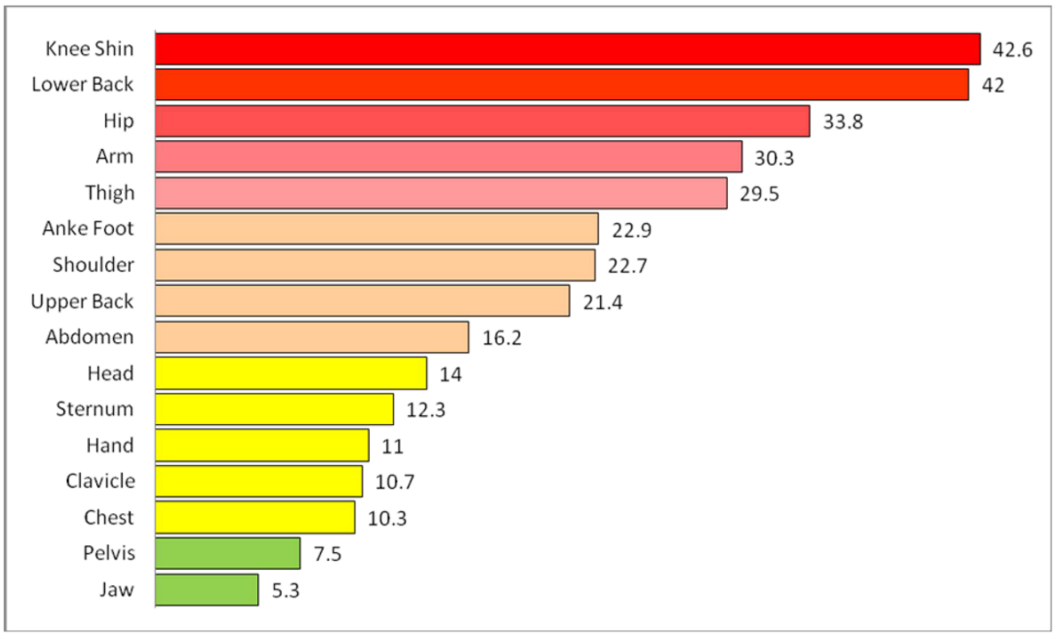

Figure 1.
Percentage of pain days that subjects hurt at each body site

Table 1

Sample Description (n=260). Reported as frequency (percent)

	Frequency (%)
Age	
16–24	32 (21.9)
25–44	156 (60.0)
45–64	47 (18.1)
Gender	
Male	102 (39.2)
Female	158 (60.8)
Genotype*	
SS	178 (70.6)
SC	61 (24.2)
Beta-thal	6 (2.4)
Beta+thal	7 (3.1)
Education	
<HS	32 (12.4)
HS	96 (37.1)
>HS	131 (50.5)
Income*	
<10,000	102 (40.2)
10,000–20,000	60 (23.6)
20,000–30,000	38 (15.0)
>30,000	54 (21.3)
Marital Status	
Married	61 (23.5)
Single	161 (61.9)
Widowed/divorced/separated	38 (14.6)
Depressed	
No	181 (69.6)
Yes	79 (30.4)

* Missing genotype on 8 subjects, income on 6 subjects

Table 2

Pain intensity and number of pain sites (Standard Error) marked on pain chart, overall and by patient or day characteristics (n=260)

		Pain intensity		Number of locations	
		Mean(SE)	p-value	Mean(SE)	p-value
Overall		4.50 (0.09)		3.3 (0.1)	
Gender	F	4.47 (0.12)	0.7010	3.4 (0.2)	0.4588
	M	4.54 (0.15)		3.2 (0.2)	
Age	<25	4.47 (0.20)	0.9843	2.7 (0.3)	0.0120
	25–44	4.51 (0.12)		3.3 (0.2)	
	45+	4.49 (0.22)		4.0 (0.3)	
Genotype[1]	SC	4.49 (0.12)	0.9856	3.6 (0.3)	0.1959
	SS	4.52 (0.21)		3.2 (0.2)	
Depression	No	4.31 (0.11)	0.0002	3.0 (0.2)	0.0111
	Yes	4.93 (0.17)		3.8 (0.2)	
Frequent Pain[2]	No	3.93 (0.14)	<0.0001	2.6 (0.2)	<0.0001
	Yes	4.93 (0.12)		3.9 (0.2)	
Crisis day	No	4.21 (0.10)	<0.0001	3.1 (0.2)	<0.0001
	Yes	5.46 (0.10)		4.2 (0.2)	
Utilization day	No	4.69 (0.12)	<0.0001	3.6 (0.2)	<0.0001
	Yes	6.60 (0.13)		4.5 (0.2)	

[1] SS or β^0 vs SC or β+ thalasemia

[2] percent pain days ≥ 67%

Table 3

Odds ratios (95% CI) of the multivariate relationship of age, gender, genotype, depression and frequency of pain to painful body sites. Specific body sites included in table if any of the 5 independent variables demonstrated a significant relationship (shown in bold).

	Age*	Female**	SS genotype**	Depressed**	Frequent Pain**
Hip	1.18 (0.99,1.39)	0.98 (0.66,1.44)	0.71 (0.47,1.07)	1.00 (0.66,1.51)	**1.48 (1.01,2.16)**
Thigh	1.00 (0.85, 1.17)	**1.60 (1.08,2.38)**	**0.66 (0.44, 0.98)**	0.91 (0.61,1.35)	**2.09 (1.41,3.08)**
Lower back	1.11 (0.93,1.31)	0.84 (0.58,1.22)	1.55 (0.99,2.43)	0.85 (0.56,1.29)	**1.87 (1.29,2.70)**
Arm	**1.19 (1.02,1.38)**	1.01 (0.70,1.46)	0.75 (0.52,1.09)	1.08 (0.75,1.55)	**1.62 (1.15,2.28)**
Ankle/foot	**1.22 (1.02,1.47)**	1.20 (0.76,1.89)	1.29 (0.83,2.00)	1.37 (0.88, 2.14)	**1.98 (1.29,3.03)**
Shoulder	**1.36 (1.13,1.64)**	0.74 (0.48,1.15)	0.67 (0.42,1.07)	0.94 (0.59,1.51)	**1.79 (1.18,2.72)**
Head	0.94 (0.73,1.20)	1.40 (0.82,2.31)	1.40 (0.78, 2.51)	**1.88 (1.15. 3.07)**	**1.73 (1.08,2.75)**
Hand	**1.40 (1.09,1.80)**	1.31 (0.76,2.25)	0.59 (0.35,1.01)	1.29 (0.77,2.18)	**2.41 (1.42,4.08)**
Clavicle	**1.41 (1.09,1.81)**	0.98 (0.55,1.73)	0.74 (0.41,1.34)	1.33 (0.72,2.44)	1.62 (0.95,2.74)
Pelvis	1.11 (0.86,1.45)	**0.50 (0.28,0.90)**	0.87 (0.41,1.85)	1.26 (0.70,2.27)	1.02 (0.52,1.97)
Knee/shin	1.07 (0.93,1.22)	1.37 (0.98,1.93)	0.91 (0.63,1.31)	0.93 (0.66,1.31)	**1.94 (1.40,2.68)**

* Odds ratio for difference of 10 years of age.

** Reference groups are: male, SC or β+ thalasemia genoptype; not depressed, percent pain days<67%

Table 4

Odds ratio (95% CI) for crisis or unplanned utilization associated with specific body sites, controlling for age, gender, genotype[1], depression and frequent pain[2]

Location		
	Crisis	**Utilization**
Lowerback	1.47 (1.26,1.71)	1.63 (1.12,2.35)
Knee/shin	1.33 (1.13,1.57)	1.52 (1.09,2.11)
Hip	1.42 (1.22,1.66)	1.42 (1.12,1.80)
Thigh	1.30 (1.08,1.57)	1.52 (1.10,2.08)
Arm	1.52 (1.26,1.84)	1.34 (1.02,1.78)
Ankle/foot	1.25 (1.06,1.47)	1.10 (0.85,1.44)
Shoulder	1.60 (1.32,1.93)	1.59 (1.21,2.09)
Upperback	1.51 (1.29,1.76)	1.49 (1.15.1.94)
Abdomen	1.42 (1.21,1.66)	1.33 (0.96,1.86)
Head	1.30 (1.09,1.55)	1.31 (0.95,1.82)
Sternum	1.65 (1.41,1.94)	2.14 (1.51,3.03)
Hand	1.38 (1.11,1.72)	1.14 (0.74,1.78)
Clavicle	1.53 (1.23,1.90)	2.13 (1.52,2.97)
Chest	1.54 (1.32,1.78)	2.43 (1.86,3.18)
Pelvis	1.54 (1.23,1.93)	1.50 (0.97,2.32)
Jaw	1.32 (1.03,1.69)	0.65 (0.42,1.00)

[1] SS or β^0 vs SC or β + thalasemia

[2] %pain days $\geq$ 67%