

## Original Research

# Utilization of Patient-Controlled Analgesia Reduces Length of Stay of Sickle Cell Crisis Hospitalizations

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## Abstract

### Background

Sickle cell crisis hospitalizations are emotionally and financially burdensome to patients and healthcare systems, and processes to decrease the frequency or length of stay of these crises should be examined.

### Methods

This is a multicenter retrospective hospital record review of sickle cell crisis hospitalizations as defined by ICD-10 codes (D57.1-4), from January 2016 through December 2019, examining inpatient medication administration records and length of stay among admitted adults aged 18–65 years. Patient controlled analgesia orders using morphine, hydromorphone, fentanyl and/or merperidine at any point of an admission (n=188) were compared to admissions without any patient-controlled analgesia orders (n=2,159). The primary end point was hospital length of stay in days. A secondary analysis examining patients with or without greater than four admissions was also conducted.

### Results

The 1,675 patients who met criteria comprised 2,347 sickle cell hospitalizations during the four years examined. Of those admissions, 188 had at least one patient-controlled analgesic documented in their chart and had an average length of stay of 4.54 days (SD 3.34). The 2,159 admissions without any patient-controlled analgesia had an average length of stay of 5.74 days (SD 4.64). The difference of 1.2 days between the groups was statistically significant ( $p \leq 0.0001$ ) using a Wilcoxon signed-rank test.

### Conclusion

Among patients with sickle cell crises who required inpatient hospitalizations, the use of patient-controlled analgesia demonstrated a statistically significant reduction of 1.2 days in their total length of stay. These findings support potentially changing hospital protocols to increase patient-controlled analgesia utilization.

### Keywords

sickle cell disease; sickle cell anemia; family medicine; sickle cell crisis; hematology; patient-controlled analgesia; hospitalization; length of stay

## Introduction

Sickle cell anemia results from homozygosity for a point mutation in the  $\beta$ -subunit of the hemoglobin (Hb) molecule ( $\beta^6$  GAG- $\rightarrow$ GTG, Glutamic acid- $\rightarrow$ Valine).<sup>1</sup> This variant hemoglobin (Hb S) polymerizes upon deoxygenation, leading to the distortion of the red blood cell (RBC) to an elongated, “sickle-like” shape. The

RBCs that contain deoxy Hb S polymer are rigid, less deformable and can cause microvascular occlusion, and also have a much-shortened lifespan compared to normal RBCs. They also interact and activate with vascular endothelium and white blood cells, leading to the generation of a chronic inflammatory state.<sup>2</sup> The combination of increased RBC destruction (hemo-

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lysis), microvascular occlusion and a chronic inflammatory state culminates in chronic organ damage involving multiple systems. Combined heterozygosity for the sickle mutation and certain other Hb variants such as Hb C, D, E and O-Arab and  $\beta$ -thalassemia can also result in different forms of sickle cell disease (SCD). The hallmark of sickle cell disease is the vaso-occlusive crisis (VOC), or painful episodes, which occur with varying frequencies in different patients. These episodes are associated with severe, excruciating pain, most commonly in the lower back, legs, arms and occasionally in the chest and abdomen. They last from a few hours to several weeks and require emergency department (ED) visits and hospitalizations. The treatment of these episodes requires parenteral opioid administration and intravenous (IV) fluids in many instances. VOCs are associated with microvascular occlusion, ischemia-reperfusion injury, increased inflammation and in certain instances can lead to more serious and life-threatening complications such as acute chest syndrome and multi-organ failure. VOCs are the most frequent cause of health care encounters in SCD patients, and account for 95% of hospitalizations in this patient population.

There are various treatment modalities currently in practice for primary prevention of VOC in sickle cell patients, including hydroxyurea L-glutamine, and more recently FDA-approved monoclonal anti-P selectin antibody, crizanlizumab (Adakveo).<sup>3</sup> Routine management with a health care provider, diet, attention to individualized triggers, optimal sleep and psychosocial support are all considered methods of primary prevention as well.

Despite primary prevention methods, acute VOCs can still occur and management is directed towards pain control and prevention of secondary complications. Pain is the most common complication of VOC in SCD and the most common reason patients seek medical care.<sup>4</sup> The National Heart, Lung and Blood Institute (NHLBI) strongly recommends as standard of care, prompt administration of parenteral opioids for severe pain within 30 minutes of ED triage.<sup>5</sup> A moderate recommendation of around the clock opioid administration by patient-controlled analgesia (PCA) has also been implemented among standards of care.<sup>6</sup> PCA appears to be preferred by patients and has a

better 72-hour discharge rate when compared to patient requested infusions of analgesia.<sup>6,7</sup> The primary purpose of this study was to reassess if PCA utilization for the management of pain reduces the overall length of stay (LOS) for patients admitted with VOC.

## Methods

### Study Design and Participants

A multicenter, retrospective, case series review was performed across 23 hospitals within HCA Healthcare's South Atlantic and East Florida divisions in the states of South Carolina, Georgia and Florida. The sampling frame included all cases of sickle cell crisis that occurred from January 2016 through December 2019. Participants were adults aged 18–65 years who had associated ICD-10 codes attributed to sickle cell crisis (ICD-10; D57.1, D57.2, D57.3, D57.4) and were admitted from the ED to inpatient status for further management. Exclusion criteria included patients admitted for a principal diagnosis not related to sickle cell crisis, and patients who did not fall within the designated age range. Physician orders, inpatient medication administration record and discharge time were reviewed to determine if PCA was used during the course of a patient's hospital stay, as well as their total LOS in days. Medications considered for PCA use were IV morphine, hydromorphone, fentanyl, oral hydrocodone and oral oxycodone. PCA may be administered either basal/continuous with demand doses or demand doses only. The electronic health record could not differentiate between the two types and the results were grouped into use of PCA or not. During an admission, PCA usage of either kind was confirmed if the medication of interest was administered following documentation of a physician order for PCA or PCA pump.

### Study Oversight and Data Collection

Permission to obtain demographic and clinical data was granted through the HCA Healthcare enterprise data warehouse (EDW) approval process in June 2019 and an institutional review board exempt determination was obtained. Data were obtained through two different electronic medical record systems: Meditech and Epic. Meditech amassed data from 22 hospitals, while Epic was exclusively used at Memorial University Medical Center in Savan-

nah, GA. The de-identified data were sent to an enterprise-level data analyst who merged and then stored the data securely in a virtual desktop interface (VDI) before granting access to a project-specific data specialist who completed statistical analysis and confirmed data validity. In February 2020, a second data request using the same process described above was completed to include all of 2019 in the data set.

### Statistical Analysis

To gain a better understanding of the patterns and trends present within the data, a series of preliminary descriptive statistics were conducted. Categorical variables were summarized using frequency counts, percentages and a series of bivariate statistics (i.e., cross tabulations) while measures of central tendency were generated for the continuous variables.

When examining the potential influence of at least one PCA administration on patients' overall length of stay, the following approach was employed: All subjects were formatted and analyzed based on the binary PCA variable (0 = no PCA during a patient's admission; 1 = at least one PCA during admission). Because we could not confirm the assumption that our primary variable of interest (overall admission LOS) was normally distributed via a Kolmogorov-Smirnov analysis, a non-parametric approach via a Wilcoxon two sample test was used to evaluate our primary research question. All inferential statistics were 2-tailed and with a tolerance for nominal type 1 error (alpha) of 0.05.

We anticipated that frequent admissions by an individual could impact their LOS; therefore, all subjects were categorized based on his/her number of unique encounters over the four-year period (2016–2019) of interest. An arbitrary delineation was assigned at greater than or equal to four unique patient admissions, where patients were then identified by the presence of at least one PCA administration during admission. All statistical analyses were performed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.).

## Results

### Study Population

The final sample was comprised of 1,675 adult individuals during the four calendar years of data collected. (Table 1) These patients accounted for 2,347 admissions across 23 hospitals in South Carolina, Georgia, and Florida (site-specific data are shown in Supplemental Table S1). Patient characteristics likely varied among the hospitals, but in general, a vast majority of individuals (n=1,588, 95%) did not receive a PCA during any encounter. If a patient received a PCA at any one of their multiple admissions they were grouped within the PCA group (n=87, 5%). There were no significant differences in average age (as determined at their first admission) between those who did or did not receive a PCA. Although there were more females included in the study (58% females versus 42% males), the PCA utilization rate overall appeared to be consistent with the utilization rate within each sex. Demographic data by similar categories, by each admission

**Table 1.** Study Population

Characteristics	Data
Total Number of Patients	1,675
Age at First Admission (median)	31.9 years
Male/Female Patients	706/969
Patients with PCA - No. (%)	87 (5.2%)
Patients without PCA – No. (%)	1,588 (94.8%)
Number of Patients with Multiple Admissions	128
Number of Patients with <4 Admissions	1,622
Number of Patients with >4 Admissions	53
Total Number of Admissions	2,347
Admissions with PCA – Yes/No	188/2,159

**Table 2.** PCA Impact on LOS in Days

PCA during Admission	No. Obs (n=2,347)	Mean	Minimum	Maximum	Median	Std Dev	Variance
No	2,159	5.74	0.09	69.65	4.67	4.64	21.52
Yes	188	4.54	0.28	18.67	3.53	3.34	11.13

instead of individual patients, are presented in **Supplemental Tables S2 and S3**.

**PCA Utilization and Length of Stay**

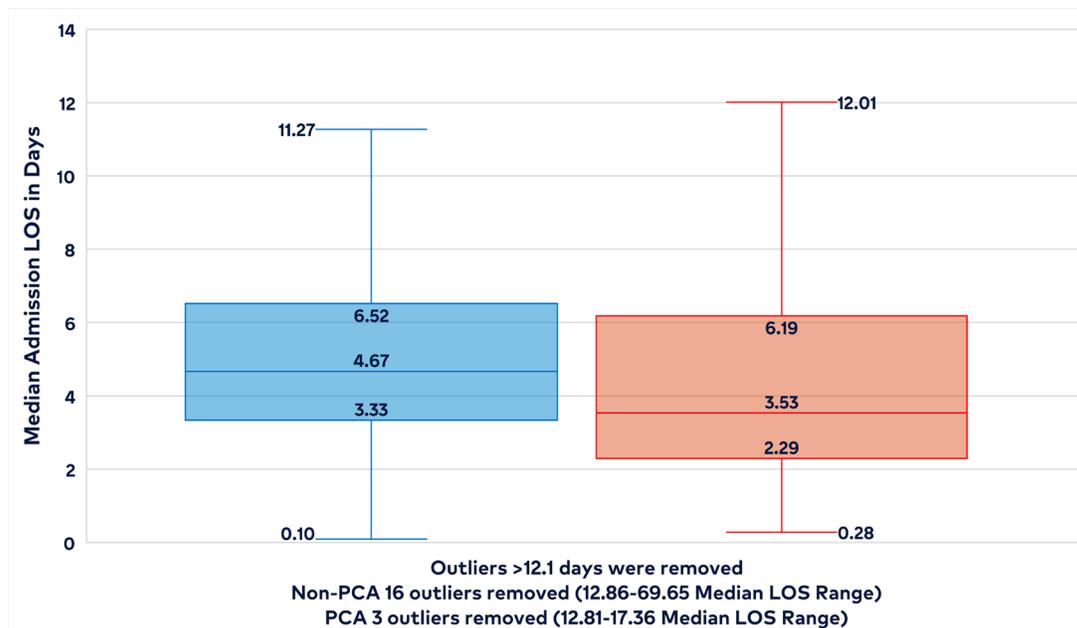
Of the total 2,347 patient encounters in question, 2,159 (92%) admissions did not show the presence of at least one PCA, while 188 (8%) admissions revealed the presence of at least one PCA. (**Table 2**) For those admissions with no presence of PCA usage, the mean LOS was 5.74 days with a median of 4.67 days. For those admissions with the presence of at least one PCA, the mean LOS was 4.54 days with a median of 3.53 days ( $p < 0.0001$ ). (**Figure 1**)

Since our primary research hypothesis was focused on the potential significant relationship between mean LOS for those admissions that did and did not receive the administration of at least one PCA, a Wilcoxon signed-rank test was computed. A series of normality tests, Kolmogorov-Smirnov and Shapiro-Wilk, were generated to look at the distribution of the PCA subgroups, no presence and presence, respectively. Since both tests rejected the presence

of normality, a non-parametric approach was used. A Wilcoxon signed-rank test p-value of  $< 0.0001$  rejected the null hypothesis of no difference between the LOS with/without PCA; therefore, we could accept that there was a difference in LOS for those encounters that did and did not receive at least one PCA.

**PCA Use with Frequent Admissions**

A secondary analysis was conducted that considered average LOS in frequent admissions by the same individual. For 1,588 patients who did not have a documented PCA administration during any of their encounters, 15 (0.9%) were admitted four or more times and had a mean LOS of 7.77 days with a median LOS of 5.59 days, while 1,573 (99%) patients were admitted fewer than four times and had a mean LOS of 5.89 days and median LOS of 4.75 days. Only 87 out of 1,675 (5%) patients utilized PCA for pain control. Among these patients, 38 (44%) were admitted four or more times and had a mean LOS of 5.29 days with a median LOS of 4.77 days, while 49 (56%) were admitted fewer than four times and had a mean LOS of 3.82



**Figure 1.** Non-PCA (Blue) Compared Against PCA (Orange) for Admission LOS - No Outliers

**Table 3.** Multiple Admissions and PCA Impact on Mean LOS in Days

PCA	Individual Patient Admissions	No. Obs	Mean	Minimum	Maximum	Median	Std Dev	Variance
No	Greater than or Equal (GE) to 4	15	7.77	2.63	27.65	5.59	6.18	38.23
	Less Than 4	1,573	5.89	0.19	69.65	4.75	4.56	20.80
Yes	GE to 4	38	5.29	1.39	13.12	4.77	2.98	8.89
	Less Than 4	49	3.82	0.31	9.25	3.45	1.93	3.71

days with a median LOS of 3.45 days. (Table 3) When comparing the higher admission frequency groups directly, there appeared to be greater PCA utilization among those individuals who were admitted more frequently. Additionally, comparing frequency groups to each other, PCA use had an approximate 2 day decrease in average LOS in both frequently and less frequently admitted patients.

### Discussion

Overall, our analysis showed that VOCs managed with PCA during a hospital admission for acute pain resulted in a shorter LOS (mean 4.5+/-3.5; median 3.3 days) versus those not receiving PCA (mean 5.7 +/-4.6; median 4.6 days). The difference, albeit modest, was significant ( $p < 0.0001$ ). The LOS is an important hospital metric for reducing cost, reducing infection risk and expediting the availability of beds and resources for incoming patients. Previous research in which PCA was compared with other methods of pain control in sickle cell crisis is limited in number and results were mixed.<sup>11-14</sup> LOS for patients in our study was significantly shorter for patients in VOC receiving PCA (mean 4.5+/-3.5; median 3.3 days) versus those not receiving PCA (5.7+/-4.6; median 4.6 days). A reviewing of the literature in which our primary outcome variable, LOS, was previously studied is inconsistent, with some authors reporting unique ancillary benefits of PCA and others disputing it. The inconsistent findings of opioid use with different methods of pain control in VOC underscores the fact that other differences between pain control methods should be considered.<sup>12,14</sup>

In order to lessen the potential confounding influence that individual patients with four or more admissions had in the overall analyses of the larger group, a secondary analysis to examine LOS among this minority revealed intriguing

results. When comparing 1,622 patients with three or fewer admissions, the analysis showed that mean LOS decreased by approximately two days in those who received the PCA (mean LOS 5.89 days versus 3.82 days), and median LOS decreased by 1.3 days (median LOS 4.75 days versus 3.45 days). Similarly, among the 53 patients who had four or more admissions, utilization of PCA decreased their mean LOS by approximately 2.5 days (mean LOS 7.77 days versus 5.29 days) and median LOS by approximately 1.2 days (median LOS 5.59 days versus 4.77). (Table 3) We theorize this result is because more frequent admissions to the same hospital could convince the admitting provider to order PCA rather than scheduling out the medications. This is likely to be especially true if the admitting provider could be primed to this action by viewing electronic medical history showing that the patient received a PCA prior during their previous admission.

Another factor that may impact LOS for sickle cell patients is the time to pain control. Other researchers have found that the ability to rapidly provide maximum opioid dose reduces LOS and those with frequent pain were more likely to benefit.<sup>15</sup> Therefore, while LOS is an important outcome variable, several other factors must be considered when considering pain management protocols for patients in VOC. Of the 23 hospital sites included in this study, only one site (Memorial Health University Medical Center in Savannah, GA) has a management protocol for treatment of sickle cell patients with VOC. (Supplemental Figure S2) This site has the greatest number of patients included in the analysis, 415 (25%) out of the 1,675 patients; accounting for 814 (34%) out of 2,347 admissions. Unfortunately, there was no consistently reliable way to track the time to PCA within the Meditech electronic health record at the other sites and therefore a comparison evaluating the protocol's effectiveness

could not be completed. Additionally, given the disproportionate number of PCA admissions coming out of this single site, a comparison of protocols at other hospitals was not feasible. (**Table S1**) It is perhaps due to Memorial's protocol that PCA utilization rate is greatest there, but this is unsubstantiated to date. Furthermore, why this single site accounted for 34% of all admissions included in the study is perplexing given that prior incidence studies within Georgia have not identified Savannah as an outlier when comparing to other cities and counties that were also included in the study.<sup>16</sup> A thorough review of how Meditech collected the data at the other sites did not yield any missing admissions. It has been suggested that populations such as sickle cell patients tend to disproportionately present to a single hospital or practice within their geographic area whose reputation is known for expertise in sickle cell care. This could explain why Memorial's Family Medicine service, who specializes in VOC care, had more admissions compared to the other hospitals surveyed, who had direct competitors with more renowned sickle cell care clinics.

While our data suggests a benefit to implementing PCA use, some limitations inherent in a retrospective review are worth noting. This retrospective study could not account for the differences in individual provider practice regarding opioid titration and discharge practices, which were not standardized. Secondly, we could not assess the methods for determining home opioid and hydroxyurea use, or general medication adherence, that may impact the frequent-pain patient admissions and LOS. Overall there are many other factors independent from pain management that can influence this metric such as psychosocial issues, opioid metabolism and tolerance, and differences in patient reported pain.

Additional prospective research should be conducted in settings of EDs, primary clinics and inpatient care of this population to better assess pain management protocols and hospital costs. Ultimately, it is the goal of family physicians to provide appropriate pain management for patients with SCD experiencing a VOC. Implementing evidence-based pain management protocols for controlling acute pain crises of SCD with PCA are necessary for improving patient-centered care and decreasing LOS.

## Conclusion

Among sickle cell patients who required inpatient hospitalizations, there was a statistically significant reduction of length of stay for those who used PCA. These findings support potentially changing hospital protocols to increase such utilization.

## Conflicts of Interest

The authors report they have no conflicts of interest.

Drs. Pallay, Prestia, Ramzan and Waldron are employees of Memorial Health University Medical Center, a hospital affiliated with the journal's publisher.

Drs. Malik and Murbach are employees of Orange Park Medical Center, a hospital affiliated with the journal's publisher.

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