Management of severe chronic pain with methadone in pediatric patients with sickle cell disease

Zachary LeBlanc1 | Chris Vance2 | Jason Payne3 | Jie Zhang4 | Lee Hilliard3 | Jeffrey D. Lebensburger1,2,3,4 | Thomas H. Howard3

1Aflac Cancer and Blood Disorders Center, Emory University, Atlanta, Georgia 
2Auburn University, Auburn, Alabama 
3Division of Pediatric Hematology Oncology, University of Alabama at Birmingham, Birmingham, Alabama 
4Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama 

Correspondence 
Zachary LeBlanc, Aflac Cancer and Blood Disorders Center, Emory University, 2015 Upper Gate Dr, Atlanta GA 30322. Email: zachary.leblanc@choa.org

Abstract 
Vasocclusive pain crises are common among pediatric patients with sickle cell disease (SCD). Some patients with repeated pain crises develop chronic pain. We performed a retrospective cohort study of pediatric patients with SCD with chronic pain treated with methadone. We identified a significant reduction in pain hospitalizations following methadone treatment (0.35 ± 0.19 vs. 0.19 ± 0.17 hospitalizations/month, P = 0.016). In addition, we did not observe overt organ toxicity nor symptoms of opioid withdrawal during methadone wean. We suggest that methadone is safe and has some clinical benefit, which should be proven in prospective randomized trials for pediatric patients with SCD and chronic pain.

KEYWORDS 
chronic pain, methadone, sickle cell disease

1 INTRODUCTION

Vasocclusive pain crises (VOC) are common complications of sickle cell disease (SCD) and contribute to decreased quality of life (QOL).1–3 Patients with frequent VOC can develop chronic pain requiring daily opioids, frequent emergency department (ED) visits, and inpatient hospitalizations. The PiSCES Study analyzed daily pain diaries from 232 patients with SCD and showed that while more than half of daily days had reported pain, only 12.7% reported a pain crisis and even fewer (3.7%) reported healthcare utilization for pain.3 In the Cooperative Study of Sickle Disease, only 1% of patients with SCD experienced more than six pain events/year requiring healthcare utilization.4 Finally, one comprehensive SCD center reported that patients with chronic pain, as compared to those without chronic pain, missed more school days, affirmed more depressive symptoms, and reported significantly decreased QOL.5 Therefore, only a small percentage of patients with SCD experience chronic pain and increased health care utilization but these patients have significant morbidity from their disease. Unfortunately, for these patients, there are limited pharmacologic interventions besides opioids and scant evidence-based nonpharmacologic strategies.

Methadone is a synthetic opioid used for chronic pain; however, lack of clear benefit and concern for toxicity may explain the limited research for its use in the pediatric SCD population. For chronic pain, we identified one cross-sectional study of 63 adults with SCD including 15 patients that had been prescribed methadone. The study did not identify a difference in pain response between short and long acting opioids but was not focused on the impact of methadone on decreasing healthcare utilization among patients with SCD experiencing chronic pain.6 For acute pain benefit, a single dose of intravenous (IV) methadone was recently shown to have improved pain scores when used in addition to standard of care pain relief strategies in hospitalized children and adult patients with SCD.7

There are concerns for methadone use worth noting, including prolongation of the QTc interval. A Finnish toxicity study identified patients treated with methadone having the highest fatal toxicity index.8 In SCD, one long-term adult study identified that a prolonged QTc was independently associated with increased mortality. However, the use of methadone was not associated with this increased risk.9 One SCD case report describes a cardiac event in a patient with SCD prescribed high dose methadone for chronic pain.10

While the risks of methadone use cannot be overlooked, there are the following several potential benefits: (1) prolonged half-life, (2) NMDA receptor antagonist (prevents typical opioid induced tolerance and hyperalgesia), (3) 50% higher oral bioavailability, and (4) less addictive properties.11 At our institution, we decided to offer methadone to treat chronic pain in patients with SCD. This retrospective review evaluates our hypothesis that daily methadone in patients with SCD...
and chronic pain will decrease acute care utilization without significant adverse effects.

2 | METHODS AND RESULTS

We conducted an institutional review board–approved retrospective cohort study of 16 patients with SCD treated with methadone for chronic pain by a single provider (TH). Patients diagnosed with chronic pain by this provider were offered methadone therapy. Patient data were recorded from 1 year prior to initiation of methadone until the patient was weaned or transitioned to adult care. We compared clinical outcomes for the pretreatment, 1 year post-treatment, and entire post-treatment periods using paired t-test. We assessed withdrawal symptoms and safety by reviewing outpatient encounters for reported withdrawal side effects. We performed electrocardiogram screening for QTc > 450 nm, estimated glomerular filtration rate (eGFR) by cystatin C to determine either a decrease in eGFR by 20% or an eGFR < 80 ml/min/1.73m², and urine microalbumin/creatinine for proteinuria.

Ten (62.5%) of the 16 patients were male and the genotypes of each patient were the following: 14 SS, one S/β⁰-thalassemia, and one SC. The mean age was 15.5 (±2.8) years at the time of methadone initiation and there was a medium follow-up of 2.1 years. Clinically, 13 (81.3%) had cholecystectomy, six (37.5%) had splenectomy, and seven (43.8%) had radiographic evidence of infarction of a long bone within the year prior to the initiation of methadone. Ten patients (62.5%) were receiving chronic transfusion during methadone and 10 (62.5%) patients received psychosocial counseling. Doses were escalated to effect with a maximum daily dose of 30 mg. The average initial dose was 12.5 mg and the mean highest dose was 26.6 mg. In 14 (87.5%) patients, the final dose was less than the highest dose and four (25.0%) patients were weaned completely off methadone. For the entire cohort, each patient spent a median of 183 days at their highest dose, a mean of 34% of the total time treated with methadone.

The average number of ED visits per month was 0.31 (±0.27) in the pretreatment period and were 0.28 (±0.28, P = 0.658) and 0.31 (±0.25, P = 0.921) in the 1 year post and entire post-treatment follow-up periods. The rate of hospitalizations per month decreased from 0.35 (±0.19) in the pretreatment period to 0.19 (±0.17, P = 0.016) and 0.22 (±0.21, P = 0.05) in the 1 year post and entire post-treatment follow-up periods.

We found no documented new abnormal QTc intervals, changes in eGFR, or new onset proteinuria during the follow-up period. There were no documented signs of opioid withdrawal.

Two patients were treated by the provider but were excluded from this cohort as their symptoms were atypical for chronic sickle cell pain. One patient with SCD, who was not followed by the provider, received methadone in the inpatient setting for the indication of opioid weaning after a prolonged intensive care unit course. This patient experienced cardiac arrest shortly after initiation of the drug and was successfully resuscitated. Investigation following this event showed a cardiac potassium channelopathy.

3 | DISCUSSION

Methadone use accomplished one goal for our program of decreasing hospitalization frequency among patients with chronic pain. However, methadone use did not significantly reduce ED visits for pain. One potential reason for this finding was that some patients required multiple ED visits in a short period of time, suggesting that the pain was a result of the same VOC. Future studies may determine whether these repeat ED visits should be viewed as independent events.

In addition to potential benefit in reducing hospitalizations, we suggest that methadone can be safely administered to patients with SCD suffering from chronic pain. Our cohort suggests that methadone can be used safely without concern for physiologic dependency, as supported by our ability to wean 84% of patients to a lower dose than their highest dose prescribed. Furthermore, the doses used in our patients were lower than those used in the drug rehabilitation setting. In addition, we did not observe drug withdrawal symptoms among patients who discontinued the drug. Our data provide additional support to a recent pediatric study of IV methadone that showed clinical efficacy and safety data.

We acknowledge several limitations inherent to a retrospective study, including a systematic prospective approach to data collection. Second, we did not incorporate QOL measures into this study. Third, we did not perform vigorous monitoring of adherence to methadone. Despite these limitations, we believe that our data suggest that methadone can improve pain for patients suffering from chronic pain and reduce hospitalizations. Safety was demonstrated in our cohort participants but cardiac toxicity should be discussed with patients prior to starting methadone. As limited evidence-based guidelines exist for chronic pain, we believe that these data support a prospective randomized trial of methadone for patients with SCD suffering from chronic pain.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Stefane Battle and Sabrina Mack-soud for their contribution of outside hospital medical record collection as part of chart abstraction for this study. We would like to thank the SCD clinical team, including our SCD CRNPs (Osborn, Dobbins, Carlton, and Evans) that care for our patients suffering from chronic pain.

CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

ORCID

Zachary LeBlanc ↗ http://orcid.org/0000-0002-0980-3374

REFERENCES


**How to cite this article:** LeBlanc Z, Vance C, Payne J, et al. Management of severe chronic pain with methadone in pediatric patients with sickle cell disease. *Pediatr Blood Cancer*. 2018;e27084. [https://doi.org/10.1002/pbc.27084](https://doi.org/10.1002/pbc.27084).