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Low-dose Ketamine for Children and Adolescents with Acute Sickle Cell Disease Related Pain: A Single Center Experience

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Abstract

Background: Opioids are the mainstay of therapy for painful vasoocclusive episodes (VOEs) in sickle cell disease (SCD). Based on limited studies, low-dose ketamine could be a useful adjuvant analgesic for refractory SCD pain, but its safety and efficacy has not been evaluated in pediatric SCD.

Procedure: Using retrospective chart review we recorded and compared characteristics of hospitalizations of 33 children with SCD hospitalized with VOE who were treated with low-dose ketamine and opioid PCA vs. a paired hospitalization where the same patients received opioid PCA without ketamine. We seek to 1) describe a single center experience using adjuvant low-dose ketamine with opioid PCA for sickle cell related pain, 2) retrospectively explore the safety and efficacy of adjuvant low-dose ketamine for pain management, and 3) determine ketamine's effect on opioid consumption in children and adolescents hospitalized with VOE.

Results: During hospitalizations where patients received ketamine, pain scores and opioid use were higher (6.48 vs. 5.99; $p=0.002$ and 0.040 mg/kg/h vs. 0.032 mg/kg/h; $p=0.004$ respectively) compared to hospitalizations without ketamine. In 3 patients, ketamine was discontinued due to temporary and reversible psychotomimetic effects. There were no additional short term side effects of ketamine.

Conclusions: Low-dose ketamine has an acceptable short-term safety profile for patients with SCD hospitalized for VOE. Lack of an opioid sparing effect of ketamine likely represents use of low-dose ketamine for patients presenting with more severe VOE pain. Prospective randomized studies of adjuvant low-dose ketamine for SCD pain are warranted to determine efficacy and long-term safety.

Keywords: Sickle cell disease; Red blood cell disorders; Hemoglobinopathies; Pain; Pain medicine; Anemia's

Introduction

Painful vaso-occlusive episodes (VOEs) are the hallmark of sickle cell disease (SCD). These episodes of recurrent pain are caused by tissue ischemia, resulting from occlusion of the microcirculation by sickled red blood cells and are the most frequent complication of (SCD) [1]. Frequency and intensity of painful episodes are variable among patients with SCD. Some patients are rarely hospitalized for pain management, while others are often admitted for treatment with intravenous (IV) opioids. These frequently hospitalized patients may have pain that is refractory to conventional therapies for multifactorial reasons, and this can lead to sub-optimal pain control and frustration for both patients and clinicians [2,3].

Traditional inpatient therapy for VOE includes IV hydration combined with administration of non-steroidal anti-inflammatory agents (NSAIDs) and IV opioids, often delivered via patient-controlled analgesia (PCA) pump [4]. Additionally, supportive care and complementary and alternative therapies have been described as helpful adjuvants in the management of SCD patients with acute painful episodes [5-10]. For frequently hospitalized SCD patients with a recurrent severe pain phenotype, this combination is not always effective in achieving pain relief. It has been hypothesized that frequent exposure to opioids in these patients could lead to tolerance and, in extreme cases, opioid induced hyperalgesia (OIH), which are thought to contribute to opioid refractory pain [11-13]. Activation of the N-methyl-D-aspartate (NMDA) receptor has been implicated in opioid

tolerance and OIH. Ketamine is an inhibitor of the NMDA receptor and has been shown to modulate opioid tolerance and OIH in both children and adults with perioperative and cancer-related pain [14-17]. While limited data is available, subanesthetic doses known as low-dose ketamine can be given as an IV bolus dose of less than 1 mg/kg or a continuous infusion at a rate of less than 1.2 mg/kg/h. At these doses ketamine does not appear to possess the sedative properties seen with higher anesthetic doses [18].

There is limited experience with the use of low-dose ketamine in SCD. Case series and case reports have documented improved analgesia, although some clinically significant side effects such as nystagmus, hypertension, dysphoria, and unresponsiveness were also noted. While most of these clinically significant side effects were associated with bolus dosing of ketamine, safety concerns remain with the use of low-dose ketamine in this population [19,20]. We here

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present our experience with the use of adjuvant low-dose ketamine in children and adolescents with SCD hospitalized for painful VOE, and provide preliminary examination of its safety and efficacy in this population through a retrospective case-crossover study design.

Materials and Methods

Research design and data sources

This study was approved by the Institutional Review Board of Children's National Medical Center. Through retrospective chart review of pharmacy records, we identified patients with SCD who had received ketamine between September 1, 2010 and May 8, 2012. We then retrospectively selected and compared two painful VOE hospitalizations for each patient separated by a maximum of 24 months. In one hospitalization the patient received adjuvant low-dose ketamine infusion in addition to opioid PCA, at the discretion of the pain medicine physician. In the other hospitalization, the patient received opioid PCA alone, without adjuvant ketamine. All patients in both groups received standard care with NSAIDs, IV hydration, and supportive care interventions.

Patients with SCD, 7-21 years old, with an admitting diagnosis of VOE, with or without an admission diagnosis of pneumonia or acute chest syndrome (ACS) were included. All demographics and hospitalization details, including pain and sedation scores every 4 hours and daily opioid administration (measured in morphine equivalents), were recorded through review of the electronic medical record (EMR). Pain scores that had been recorded using either the Numeric Rating Scale (NRS) or the Wong-Backer Faces Scale, and sedation scores that had been assessed utilizing The University of Michigan Sedation Scale (UMMS) were documented during the chart review [21,22]. Comorbidities such as history of asthma, priapism, kidney disease, or avascular necrosis, were also recorded from the EMR.

Endpoints

Our primary endpoint to assess efficacy of adjuvant ketamine was daily opioid consumption during the hospitalizations. We compared the hospitalizations with and without adjuvant ketamine to determine a possible opioid-sparing effect of ketamine. To convert total daily opioid dose to IV morphine equivalents we used the following conversions: codeine to oral morphine (10:1), oxycodone: oral morphine (1:1.5), oral morphine: IV morphine (3:1), IV/oral hydromorphone: IV/oral morphine (5:1), tramadol: oral morphine (5:1), oral methadone: oral morphine, (1:4), oral methadone : intravenous methadone (2:1) [23,24]. Short term safety was assessed by recording when and if adjuvant low-dose ketamine infusion was discontinued due to a suspected adverse event as documented in Pain Medicine progress notes. The sedative effect of adjuvant low-dose ketamine was assessed by noting recorded sedation scores. Secondary endpoints assessed through chart review included pain and sedation scores, administration of anti-emetics and antihistamines, and use of complementary and alternative therapies. Use of alternative pain management agents was defined as administration of gabapentin, pregabalin, duloxetine, fluoxetine, diazepam, or lorazepam and was also assessed through chart review.

Data management and analysis

All study data was managed in REDCap electronic data capture tools hosted at Children's National Medical Center [25]. The data was exported from REDCap to SAS 9.2 (SAS Institute, Cary, NC) for statistical analysis. We compared demographic and clinical characteristics of patient hospitalizations when they were treated

with and without ketamine using univariate frequency distributions. Exploratory bivariate analyses (McNemar's test and paired t-test for significant differences between paired samples) were used to compare variables between the paired hospitalizations. Multiple linear regressions was used with the continuous dependent variable of mean opioid use to attempt to control for key confounders including diagnosis of ACS, red blood cell transfusion, number of painful sites, pain score, and length of stay.

Results

Thirty-three paired hospitalizations that occurred between October 2008 and April 2012 met the study eligibility criteria. Demographic data reflective of the time of presentation for the PCA and ketamine hospitalization is presented in Table 1. The mean age of our patients was 15.6 years (range 7.5-21.4 years) and 67% were females. The mean duration until low-dose ketamine started was 1.17 days, with the majority of patients having low-dose ketamine added on hospital day 2 or 3. The mean interval time between a patient's 2 hospitalizations was 5.4 months (\pm 4.5 months, range=0.25 -19.3 months). We collected data on 242 paired inpatient days between the two hospitalizations. Twenty-six out of 33 patients (79%) had the PCA alone hospitalization before their PCA and ketamine hospitalization. Average number of hospitalizations in the 6 months prior to presentation for their PCA and adjuvant ketamine hospitalization was 2.1, and 21/33 patients (64%) had \geq 2 hospitalizations in the 6 months prior. Low-dose ketamine was administered as a continuous infusion (0.1 mg/kg/h) for a mean duration of 3.11 days (\pm 2.29 days, range 0.8-11.91 days). In one patient, low-dose ketamine was temporarily escalated to a dose of 0.15 mg/kg/h.

Three patients (9%) had their low-dose ketamine infusion discontinued or dose decreased due to a perception of an adverse effect

Age	
Mean (range)	15.6 years (7.5-21.4)
Gender	
Female	22 (67%)
Phenotype	
SS	23 (70%)
SBeta0 Thalassemia	1 (3%)
SC	8 (24%)
SBeta+Thalassemia	1 (3%)
Co-morbidities	
Asthma or hx of severe ACS	23 (70%)
Avascular Necrosis	5 (15%)
Iron overload	3 (9%)
Kidney Disease/HTN	6 (18%)
Priapism	1 (3%)
Hydroxyurea therapy	
Yes	12 (42%)
Average dose	22.74 mg/kg/day
Time to Ketamine start (\pm SD (range))	1.17 days (\pm 0.99) (0.09-3.56)
PCA type	Morphine 21 (64%)
Hydromorphone 12 (36%)	
Day Ketamine Added	HD 1 (n=6)
	HD 2 (n=13)
	HD 3 (n=7)
	HD 4 (n=6)
	HD 5 (n=1)
Total Duration of Ketamine (\pm SD)	3.11 days (\pm 2.29)

hx=history ACS=Acute Chest Syndrome, HTN=Hypertension, HD=hospital day

Table 1: Demographic Characteristics of Ketamine+PCA group. n=33 patients.

on the part of the patient, parent, or physician. The patient whose dose was increased to 0.15 mg/kg/h experienced vivid dreams, for which the infusion was decreased back to 0.1 mg/kg/h with resolution of the adverse effect. One patient had delusions after starting the low-dose ketamine infusion. This effect was believed to be multifactorial and was managed by discontinuation of both the low-dose ketamine infusion and the continuous infusion of the opioid PCA, as well as administration of a red blood cell transfusion for severe anemia. The patient's symptoms resolved after these interventions. The third patient had the low-dose ketamine infusion discontinued after 19.6 hours due to the patient's complaint of feeling "dizzy" and the lack of effect perceived by the patient and family. There were no cardiac toxicities noted. Mean daily sedation score during the opioid PCA/low-dose ketamine hospitalization was 0.277 (range 0-1.8) vs. 0.173 (range 0-1.6) in the opioid PCA hospitalization, $p=0.078$. Disease severity and hospitalization characteristics for each patient, and then by patient days are presented in Tables 2 and 3. Mean daily pain scores in the opioid PCA/low-dose ketamine hospitalization was higher at 6.48 vs. 5.99 in the opioid PCA alone hospitalization ($p=0.002$). More patients had concurrent ACS during the opioid PCA+ ketamine hospitalization vs. the opioid PCA alone hospitalization (42% vs. 15%, $p=0.013$). The use of supportive care and complementary therapies during the two hospitalizations are described in Figure 1.

Mean opioid use during the opioid PCA/low-dose ketamine hospitalization and opioid PCA only hospitalization was 0.040 (\pm SD 0.011) and 0.032 (\pm SD 0.012) mg/kg/h morphine equivalents respectively ($p=0.0038$). Attempts were made to adjust for confounders impacting opioid use including, ACS, red blood cell transfusion, transfer to ICU, number of painful sites, and mean pain score through multiple linear regressions. There was no change in the mean opioid use after adjustment; therefore only crude opioid use is reported.

Discussion

We describe our experience with adjuvant low-dose ketamine therapy in children and adolescents with SCD and compare

	PCA+ ketamine	PCA	change	p-value
Length of stay (days) (range)	5.6 (2.5-13.7)	4.4 (1.7-8.8)	1.21	0.042°
Mean pain score on DOA	7.84 (3.5-10)	7.25 (3-10)	0.57	0.078°
Mean daily pain score	6.48 (0-10)	5.99 (0-10)	0.46	0.002°
Mean daily sedation score	0.277 (0-1.8)	0.173 (0-1.6)	0.12	0.078°
Duration of PCA (\pm SD)	4.37 days (\pm 2.5)	3.4 days (\pm 1.5)	22.5 hrs	0.050°
Concurrent ACS n (%)	14 (42%)	5 (15%)		0.013+
ICU transfer n (%)	3 (9%)	1 (3%)		0.317+
RBC transfusion n (%)	12 (36%)	7 (21%)		0.059+

DOA=day of admission, ACS=Acute Chest Syndrome, ICU=intensive care unit
°paired t-test, *McNemars test

Table 2: Comparison of Hospitalization Characteristics n=33.

	PCA+ ketamine	PCA	p-value+
Days with pain score \geq 8	146/235 (62%)	133/240 (55%)	0.113
Number of painful sites	\geq 2=54%	\geq 2=45%	0.060
	\geq 3=20%	\geq 3=7%	0.0001
Received Antiemetic	24/240 (10%)	33/241 (14%)	0.228
Received Antihistamine	79/240 (33%)	63/242 (26%)	0.060

*McNemars test

Table 3: Hospitalization characteristics and severity by patient days (n=242 patient days).

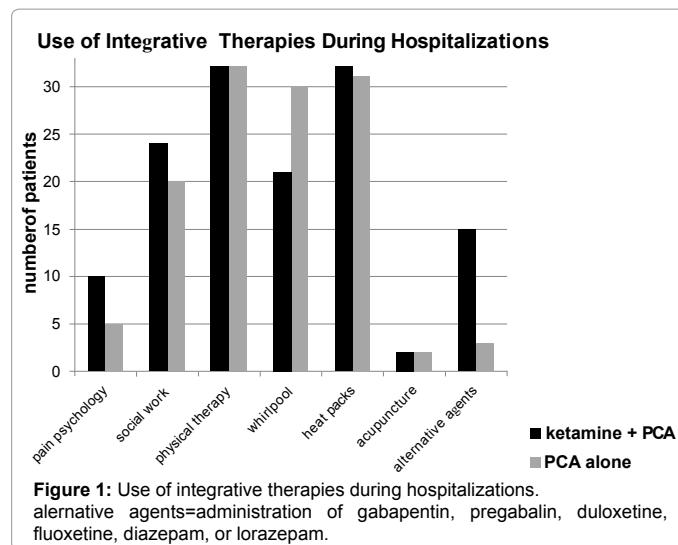


Figure 1: Use of integrative therapies during hospitalizations. alternative agents=administration of gabapentin, pregabalin, duloxetine, fluoxetine, diazepam, or lorazepam.

characteristics of hospitalizations with and without ketamine use. Ketamine was safe, in the short term, when given as continuous infusion of 0.1 mg/kg/h as an adjuvant to opioid PCA in children and adolescents with SCD hospitalized for VOE. Psychotomimetic effects were infrequent and were reversible with discontinuation of the infusion. While sedation scores were statistically different, average sedation score in both groups ranged from 0-1 (awake to mildly sedate) indicating no clinically significant differences in sedation between the two groups. As observed in other studies, although not statistically significant, a trend is seen with fewer anti-emetics used by patients receiving ketamine [26,27]. In comparison to prior studies, the lack of major adverse effects suggests that the delivery method and dose used in this study may have a more favorable side effect profile than bolus dosing for pediatric SCD patients. Prior case series describing five patients with SCD receiving low-dose ketamine reported one patient who experienced nystagmus, hypertension, and unresponsiveness after transition to a new infusion which was hypothesized to have caused an inadvertent bolus dose. Another patient in that same case series complained of dysphoria after the initial ketamine bolus and asked that drug is discontinued [19]. Due to our study design we are not able to comment on the long term effect of ketamine, more specifically neuroapoptosis, which has been recently raised as major concern and potentially results from the exposure of the developing brain to ketamine [28-30].

We did not observe an opioid sparing effect of low-dose ketamine in this group of frequently hospitalized patients. In fact, opioid requirement was higher during the admission when low-dose ketamine was prescribed. The reasons for this finding could be multifactorial in this retrospective study. Higher opioid use in the PCA and low-dose ketamine group could be due to a more severe painful crisis experienced by patients during their low-dose ketamine/opioid hospitalization. This is suggested by higher pain scores and increased number of painful sites during those hospitalizations. The presence of higher pain scores and increased opioid use in the low-dose ketamine/opioid PCA hospitalizations is in concert with our Pain Medicine group's practice of adding ketamine for patients with more difficult to manage painful episodes. Furthermore, higher rates of ACS and need for red blood cell transfusion may also be indicators of a more severe painful crisis. Most patients had their adjuvant ketamine hospitalization at an older age which could also be suggestive of progression to more severe disease overtime. The increased number of painful sites noted during low-dose ketamine admissions could also reflect progression towards a

chronic pain phenotype. The mean age of our patients was older than previously described cohorts of patients with SCD, which could suggest that older patients are more likely to exhibit evidence of a chronic pain phenotype and poor responsiveness to opioids leading physicians to seek additional therapies such as low-dose ketamine [31-33]. Our study population experienced much higher utilization of physical therapy services, whirlpool, and heat packs than previously reported [33]. Additionally, higher usage of neuropathic and other alternative pain management agents were recorded in a statistically significant number of patients during their ketamine hospitalization which may indicate the severe and refractory nature of their pain, which likely led to low-dose ketamine administration. Patients with hemoglobin SC disease, generally considered to have milder disease, also received ketamine for pain demonstrating presence of this severe pain phenotype across the SCD genotypes.

Our study population is also remarkable in that about two thirds of our patients had at least 3 hospitalizations in 6 months indicating that our sample represents a group of frequently hospitalized patients with severe disease. Prior studies have shown wide variability in the frequency of painful VOs requiring hospitalization. About 5% of patients average 3-10 hospitalizations per year for painful crisis, accounting for 33% of episodes treated by physicians [3]. Our study group also likely reflects the poorly compliant adolescent patients, since only 36% of our study patients were receiving hydroxyurea at the time of hospital admission, although given the combination of frequent hospitalizations and high rates of ACS these patients are likely prime candidates for hydroxyurea therapy [34].

We conclude that for difficult to control pain in children and adolescents with SCD hospitalized for VOE, low-dose ketamine infusion has an acceptable short-term safety profile and may be used an adjuvant to opioids. We were unable to detect an opioid sparing effect of ketamine in our population which is likely attributable, at least in part, to the increased severity and chronicity of pain in the PCA plus low-dose ketamine hospitalizations. We cannot comment on the efficacy of the regimen due to selection bias introduced by our retrospective non-randomized case-control design, where adjuvant ketamine was prescribed at the discretion of the treating physician. Additionally, with a relatively small sample size we were unable to control for disease severity, pain scores, opioid use, and SCD-related complications, and pharmacogenetic variations which further impairs our ability to comment on the efficacy of adjuvant ketamine. Further studies, including a large prospective randomized control trial that could address the above mentioned challenges, are necessary to determine the safety and efficacy of adjuvant ketamine to opioid PCA for patients with SCD. Efficacy studies should also include long-term safety assessment.

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Conflict of Interest Statement

There were no specific funding sources for this study. The authors have no relevant conflicts of interest to disclose. The study discusses off label use of the drug ketamine.

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