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RESEARCH ARTICLE

Ketamine use for management of vaso-occlusive pain in pediatric sickle cell disease

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Abstract

Background: Typical sickle cell disease (SCD) vaso-occlusive pain episode (VOE) management includes opioids, which are often inadequate and can be associated with significant side effects. Ketamine, a dissociative anesthetic, is a potentially effective adjunct to VOE management.

Objectives: This study aimed to characterize ketamine use for VOE management in pediatric SCD.

Method: This retrospective case series summarizes a single-center experience regarding the use of ketamine for inpatient management of pediatric VOE in 156 admissions from 2014 to 2020.

Results: Continuous low-dose ketamine infusion was most commonly prescribed to adolescents and young adults as an adjunct to opioids (median starting dose 2.0 μg/kg/min; median maximum dose 3.0 μg/kg/min). Ketamine was started a median of 13.7 hours after admission. Median ketamine infusion duration was 3 days. In most encounters, ketamine infusion was discontinued prior to opioid patient-controlled analgesia (PCA) discontinuation. The majority of encounters (79.3%) had a reduction in either PCA dose, continuous opioid infusion, or both while receiving ketamine. Low-dose ketamine infusion was associated with side effects noted in 21.8% (n = 34) of encounters. The most common side effects included dizziness (5.6%), hallucinations (5.1%), dissociation (2.6%), and sedation (1.9%). There were no reports of ketamine withdrawal. Most patients who received ketamine went on to receive it again during a subsequent admission.

Conclusion: Further study is needed to determine the optimal timing of ketamine initiation and dosing. The variability of ketamine administration highlights the need for standardized protocols for ketamine use in VOE management.

KEYWORDS
pain, pediatrics, sickle cell disease (SCD), vaso-occlusive episode (VOE)

Abbreviations: EMR, electronic medical record; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PCA, patient-controlled analgesia; SCD, sickle cell disease; VOE, vaso-occlusive episode.

1 | INTRODUCTION

Sickle cell disease (SCD) can cause many complications including recurrent vaso-occlusive episodes (VOEs) of pain. Acute VOEs are defined as new onset of pain lasting at least 4 hours for which there is no alternative explanation.[1] VOE pain is often excruciating and is a significant cause of morbidity for patients with SCD.[2,3]

VOE pain can be difficult to manage even with continuous opioid infusions and around-the-clock nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.[4] Typical management of VOE pain includes opioids, which can be administered orally at home or parenterally using patient-controlled analgesia (PCA) and continuous intravenous (IV) infusions while hospitalized. Currently, NSAIDs and opioids are the mainstay of inpatient VOE management. The National Heart, Lung, and Blood Institute (NHLBI) guidelines recommend an individualized prescribing protocol written by the patient's SCD provider. For severe pain, parenteral opioids are recommended with frequent re-assessment and dose adjustment as necessary, as well as continuation of oral NSAIDs as an adjuvant analgesic in the absence of contraindications.[5] Similarly, the American Society of Hematology (ASH) 2020 guidelines recommend rapid assessment and administration of analgesic with frequent re-assessment to optimize pain control. For patients in whom opioid therapy is indicated, ASH guidelines suggest tailored opioid therapy on a patient-specific basis and also suggest a short course of NSAIDs in addition to opioids for acute pain management.[6] Opioids can be administered in a variety of modalities including orally, nasally, subcutaneously, topically, and intravenously as continuous infusions, boluses, or via PCA. A variety of other interventions such as lidocaine patches, hydration, heat, Reiki, massage, and cognitive behavioral therapy are also important adjunctive components to pain management.[7–10]

However, VOE pain is often unresponsive even to continuous high-dose IV opioid via PCA.[11] Opioid-induced side effects such as nausea, constipation, pruritis, and sedation are common among children, adolescents, and adults.[12–16] Serious adverse effects such as severe respiratory depression are less common and may be affected by comorbidities, very young age, and drug interactions.[17,18] Furthermore, recurrent opioid use over time can lead to the development of opioid tolerance and opioid-induced hyperalgesia, both of which can make opioids less effective at providing VOE pain relief.[19] Due to these side effects and the potential for development of opioid tolerance, there is an urgent need for additional opioid-sparing agents for pain management in SCD. NSAIDs are also currently used as a mainstay of VOE management, but these medications are sometimes insufficient in capturing pain and are associated with risk of nephrotoxicity, which is far from ideal in patients with SCD who have a disease-associated risk of kidney injury over time.[20]

Ketamine, a dissociative anesthetic, is a potentially effective adjunct to current VOE management.[21] Ketamine produces potent analgesic effects by blocking N-methyl-D-aspartate (NMDA) receptors, which impairs sensitization of spinal neurons to nociceptive stimuli. This mechanism allows ketamine to mitigate neuropathic pain and modulate opioid tolerance and opioid-induced hyperalgesia.[22,23] Although only FDA-approved for use as an anesthetic agent, limited data suggest that low-dose ketamine is a safe and potentially effective treatment for VOE pain.[24,25] This report describes the use of low-dose ketamine infusion for management of VOE pain among pediatric patients with SCD.

2 | METHODS

This single-center retrospective case series study was approved by the hospital's Institutional Review Board. Retrospective chart review was performed to collect data regarding the use of ketamine for inpatient management of VOE pain in pediatric patients with SCD from 2014 to 2020 at a quaternary-care pediatric hospital. We queried the hospital electronic medical record (EMR) using an informatics platform managed by the Information Services Department. We initially identified all inpatient admissions to the hematology service between January 1, 2014 and December 31, 2020, with at least one primary diagnosis code related to SCD VOE (ICD-10: D57.0*, D57.21*, D57.41*, D57.43*, D57.45*, D57.81*; ICD-9: 282.42, 282.62, 282.64, 282.69). Encounters were excluded if the patient did not receive a ketamine infusion during the admission. Demographic and clinical information was obtained from chart reviews of the hospital EMR.

2.1 | Demographic information

Patient age, gender, ethnicity, race, and SCD genotype were collected from the EMR. Fetal hemoglobin within 1 year prior to the first admission in which a patient received ketamine was recorded. Similarly, the number of admissions for VOE in our hospital within 1 year prior to first admission with ketamine was counted. For each admission, we collected data regarding the patient's current and prior SCD disease-modifying treatments and whether the patient had received chronic red blood cell transfusions.

2.2 | Ketamine administration

Ketamine infusion was administered as an adjuvant to opioids. All doses of ketamine administered during the admission were included in the analysis. Using the timestamp of each administration, we then calculated the following: (a) time to ketamine start; (b) duration of ketamine infusion; (c) initial, maximal, and final dose of ketamine in μg/kg/min; and (d) bolus administration and titration of the dose before stopping.

2.3 | Side effects

Each encounter in which a patient received ketamine was reviewed to evaluate the following: (i) presence of ketamine side effects, including time, dose, and patient condition when side effects presented;

(ii) concomitant administration of benzodiazepines; and (iii) signs and symptoms of withdrawal from ketamine including cravings for the drug, mood swings, anxiety, insomnia, sweating, and heart palpitations.

2.4 | Data analysis

We present descriptive data for demographics, ketamine infusion information, and side effects. Additional narrative descriptions of the side effects are presented. All analyses were performed in R version 4.1.3.[26]

3 | RESULTS

We identified 1268 encounters of patients with SCD who were admitted with VOE over 6 years. Of those, we identified 156 (12.3%) encounters in which 44 unique patients received ketamine. Demographic information regarding these patients can be found in Table 1. Most patients who received ketamine were adolescents and young adults, and most patients had genotype HbSS.

3.1 | Encounters with ketamine administration

There were 156 encounters in which patients received ketamine. Ketamine infusion was started a median of 13.7 hours after admission (interquartile range [IQR] 7.4–28.8) and 9.7 hours (IQR 3.9–25.3) after PCA initiation. Median starting infusion rate was 2.0 μg/kg/min (IQR 1.98–2.01). There was a median of one ketamine dose increase per admission (IQR 0–2). Median maximum ketamine infusion rate was 3.0 μg/kg/min (IQR 2.0–4.0) (Figure 1). Median duration of ketamine infusion was 3.0 days (IQR 1.8–4.3). There were 17 encounters in which ketamine infusion lasted less than 1 day. In 12 of these cases, there were no reported side effects. In 81 encounters (51.9%), the maximum ketamine dose was lower than the final dose. In 33 (21.2%) encounters, the ketamine dose was decreased within 6 hours prior to discontinuation.

3.2 | Opioid PCA orders

In all admissions but one, patients received IV opioid PCA. The type of opioid administered was hydromorphone in 106 encounters, morphine in 21 encounters, and fentanyl in seven encounters. There were 21 additional encounters in which two opioids were administered, 19 of which included both hydromorphone and morphine, and two of which included both hydromorphone and fentanyl. The timing of opioid dose adjustment relative to ketamine infusion was variable. In two admissions (1.3%), IV opioid was discontinued before ketamine initiation. In 32 admissions (20.6%), no changes were made to opioids during ketamine infusion. In 123 admissions (79.3%), the opioid dose was decreased during ketamine infusion. In 57 admissions (36.7%), both the continuous and bolus components of IV opioid were decreased during ketamine infusion. In 50 admissions (32.3%), only the continuous opioid infusion dose was decreased during the ketamine infusion. In 16 admissions (10.3%), only the bolus dose of the opioid infusion was decreased during the ketamine infusion. For admissions in which opioid was decreased during ketamine infusion, the median time from start of ketamine infusion to first opioid dose adjustment was 12.5 hours (IQR 3.25–36.6). In most encounters (n = 119, 76.3%), ketamine infusion was discontinued prior to discontinuation of opioid PCA.

TABLE 1 Characteristics of patients admitted with VOE and treated with ketamine.

Characteristics *N* (%) or median [IQR]	All patients (*N* = 44)
Age at first ketamine admission (years)	18.0 (14.9–20.0)
Sex	
Female	25 (56.8)
Ethnicity	
Hispanic or Latino	10 (22.7)
Not Hispanic or Latino	31 (70.5)
Unknown	2 (4.5)
Missing	
Race	
White	2 (4.5)
Black	33 (75.0)
Other	9 (20.5)
Genotype	
Hb SS	30 (68.2)
Hb SC	10 (22.7)
Hb S beta thal 0	4 (9.1)
Fetal hemoglobin within 1 year prior to first admission with ketamine	8.8% (6.0–13.1)
Number of admissions for VOE within 1 year prior to first admission with ketamine	1 (0.0–3.0)
Treatments ongoing at time of first admission with ketamine	
Hydroxyurea	31 (70.5)
Crizanlizumab	0 (0.0)
Voxelator	0 (0.0)
Number of ketamine admissions per patient	2 (1–5)
Length of stay (days) of first ketamine admission	5.9 (5.1–7.9)

Abbreviations: IQR, interquartile range; VOE, vaso-occlusive episode.

3.3 | Side effects

Side effects were noted in 21.8% (n = 34) of admissions. The most experienced side effects included altered mental status

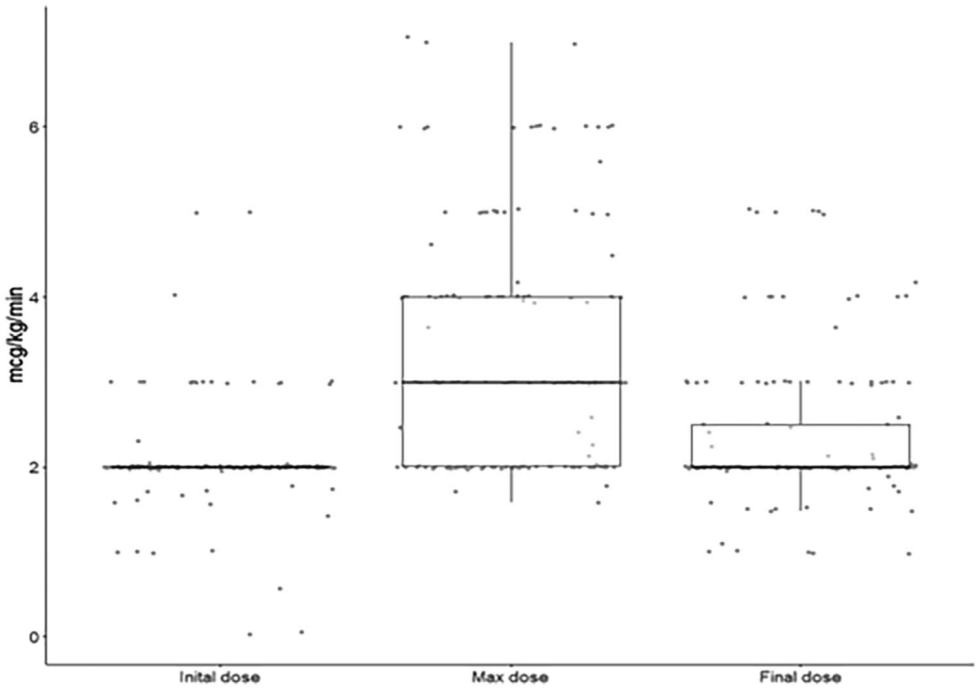

FIGURE 1 Ketamine dose over time.

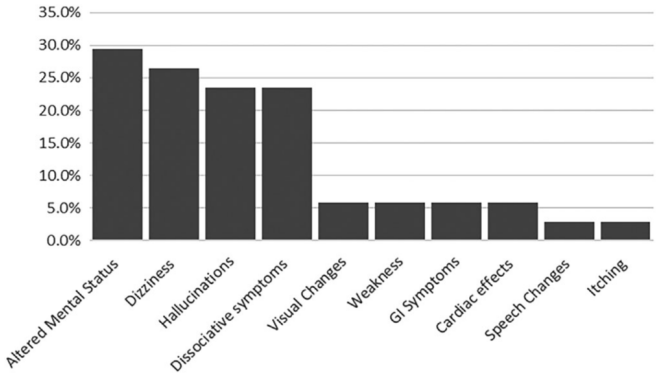

FIGURE 2 Frequency of side effects as a percentage of encounters in which side effects were reported.

(n = 10, 6.4%), dizziness (n = 9, 5.6%), hallucinations (n = 8, 5.1%), dissociative symptoms (n = 8, 5.1%), and sedation (n = 3, 1.9%) (Figure 2). The median ketamine infusion rate at which side effects were noted was 3 μg/kg/min (IQR 2.0–4.0). Ketamine was discontinued due to side effects in 23 cases (67.6% of cases in which side effects were reported); in two of the 23 cases, the ketamine was discontinued and then resumed at a decreased dose, and in four cases the dose was decreased and then discontinued. In nine (26.5%) cases, ketamine infusion rate was decreased due to side effect, but the infusion was not discontinued. Median decrease due to side effect was 1 μg/kg/min (IQR 1.0–2.0), with a median dose reduction of 33% (IQR 26.7–55.0) of dose at which side effect was experienced. Of the 14 encounters in which rate was decreased due to side effect, 11 (78.6%) resolved within 24 hours. Of the 22 encounters in which infusion was discontinued due to side effect, 21 (95.5%) resolved within first 24 hours.

For 87% (n = 136) of the admissions during which ketamine was administered, the patient had a subsequent admission for VOE. In 98 (72.1%) of cases, patients received ketamine during their next admission for VOE. Patients were more likely to receive ketamine during a subsequent admission for VOE if they had not experienced a side effect during their previous ketamine infusion (un-adjusted OR: 2.3, p-value = .054).

When comparing encounters in which side effects were reported to those in which they were not, there is no significant difference in patient sex or age at admission between groups. There was a significant difference in hemoglobin genotype between groups (p = .005). In both groups, most patients had hemoglobin SS. However, a higher percentage of encounters with side effects included patients with hemoglobin SC. Furthermore, a higher percentage of patients in the no-side effect group received hydroxyurea before admission (p = .032; Table 2).

3.4 | Benzodiazepines and withdrawal

In 11 (7.1%) encounters, benzodiazepines were administered during ketamine infusion: seven as IV doses and four as enteral doses. Benzodiazepines were administered within 12 hours after ketamine initiation in only three cases. There were no cases in which benzodiazepines were administered after discontinuation of ketamine. In most cases (n = 5, 45.5%), benzodiazepine was given for anxiety, in two (18.2%) cases for spasticity, two (18.2%) for spasm, one (9.1%) for agitation, and one (9.1%) for pain. There was no report of signs or symptoms of ketamine withdrawal during any of the admissions.

TABLE 2 Characteristics of admissions with and without ketamine side effects.

Characteristics *N* (%) or median [IQR]	Encounters with SE (*N* = 34)	Encounters without SE (*N* = 122)	*p*-Value
Age at admission	16.45 [13.65–18.50]	17.95 [15.10–20.88]	.055
Patient sex			
Female	24 (70.6)	76 (62.3)	.491
Patient genotype			
Hb SS	25 (73.5)	103 (84.4)	.005
Hb SC	8 (23.5)	7 (5.7)	
Hb S beta thal 0	1 (2.9)	12 (9.8)	
Chronic transfusion			
Yes	1 (2.9)	15 (12.3)	.204
Treatments before admission with ketamine			
Hydroxyurea	24 (70.6)	107 (87.7)	.032
Crizanlizumab	0 (0.0)	6 (4.9)	.415
Treatments ongoing at admission with ketamine			
Hydroxyurea	24 (70.6)	97 (79.5)	.384
Crizanlizumab	0 (0.0)	6 (4.9)	.415
Benzodiazepines during admission			
Yes	4 (11.8)	7 (5.7)	.011
Length of stay (days) of first ketamine admission, median [IQR]	6.31 [4.53–9.20]	5.44 [4.00–7.80]	.13

Abbreviations: IQR, interquartile range; SE, side effects.

4 | DISCUSSION

We report a reduction in either PCA opioid dose, continuous opioid infusion, or both in 79.3% of admissions in which patients concurrently received continuous ketamine infusion. Furthermore, in 20.6% of admissions there was no further increase in opioid dose after initiation of ketamine. These findings suggest that individuals may experience benefit from low-dose ketamine infusion, but future studies are needed to determine whether low-dose ketamine infusion is opioid-sparing.

There is an urgent need for adjunctive therapies to better manage SCD VOE pain, particularly for the many individuals with pain severe enough to require hospitalization. Opioids are a mainstay of VOE management, but are associated with numerous side effects and potential for development of opioid tolerance, so there remains a pressing need for adjunctive agents for VOE management. The ASH 2020 guidelines for management of acute and chronic pain in SCD provide a conditional recommendation that a subanesthetic (analgesic) ketamine infusion can be used as an adjunctive treatment of pain for adults and children who are hospitalized with acute SCD-related pain that is not effectively treated with opioids alone. This recommendation is conditional given the very low certainty in the evidence of effects.[6]

Here, we report the use of low-dose continuous IV ketamine infusion for VOE pain in the inpatient setting. Patients who received ketamine infusion for VOE were most commonly adolescents and young adults, and most patients received ketamine infusion as an adjunct to IV opioids. Benzodiazepines were not typically administered with ketamine infusions. Most individuals in this study received a low-dose ketamine infusion, with a median starting dose of 2 μg/kg/min (0.12 mg/kg/h) and a maximum infusion dose of 3 μg/kg/min (0.18 mg/kg/h). By comparison, typical starting doses reported in the literature range from 0.025 mg/kg/h (0.4 μg/kg/min) to 0.3 mg/kg/h (5 μg/kg/min).[24]

The median time at which ketamine was initiated was more than 12 hours after admission and 9.7 hours after PCA initiation. In most patients with VOE, the episode is preceded by a prodromal phase lasting 1–2 days, followed by peaking of pain on day 3, and a duration until approximately day 6 or 7 before resolving.[27] In a recent study in adults with SCD, initiation of ketamine within 3 days of admission was associated with a significant decrease in patient-reported pain.[28] More data are needed to determine whether ketamine infusion should be started at the time of opioid PCA initiation or whether ketamine initiation should be deferred until after it has been determined that opioids are not adequately capturing a patient's pain. Emergency department studies showing a reduction in opioid use and pain when ketamine is given with morphine for acute pain suggest a benefit to ketamine initiation at the time of PCA initiation, but those patients may have more side effects.[29]

Opioid PCA management during ketamine infusion was variable, but in most cases opioid doses were decreased during ketamine infusion. In most encounters, ketamine was discontinued prior to discontinuation of opioid PCA. However, it is not possible to know from this study alone whether initiation of ketamine resulted in decrease in total daily

opioid requirement, which is a limitation of this study design. Additional future studies are necessary to determine whether initiation of low-dose ketamine infusion results in a decrease in total daily opioid requirement. In this single-institution study, ketamine use was variable, with differences noted in the timing of initiation and discontinuation relative to opioids as well as ketamine starting doses and dose adjustment patterns. This variability highlights the need for standardized protocols to guide ketamine use for VOE (Figure S1).

The majority of patients who received ketamine infusions for VOE did not experience short-term side effects. Side effects were reported during nearly 22% of admissions, similar to the rate seen in a smaller adult case series.[30] The most common side effects experienced by patients receiving continuous ketamine infusion included altered mental status, dizziness, hallucinations, and dissociative symptoms, which are comparable to side effects noted with low-dose ketamine infusion in the literature.[24] In our cohort, gastrointestinal (GI) symptoms included nausea and cardiac symptoms included hypertension and bradycardia. Notably, these side effects occurred despite the low median rates of ketamine infusion administered. Nearly all short-term side effects were reversible, resolving within 24 hours of dose reduction (n = 11, 78.6%) or infusion discontinuation (n = 21, 95.5%). However, there is a paucity of data regarding long-term side effects of low-dose ketamine infusion, particularly in terms of potential effects on the developing brain. No patients experienced ketamine withdrawal symptoms after ketamine discontinuation. Most patients who received ketamine once went on to receive it again during a subsequent admission for VOE.

Based on this retrospective case series, it seems that continuous ketamine infusion may be a safe and useful adjunct to IV opioids for inpatient VOE management. Ketamine infusion should be considered when developing individualized pain plans for patients with SCD, and it may be particularly beneficial for individuals who have experienced inadequate pain relief from opioids in the past or who have a history of dose-limiting opioid side effects.

Further prospective study is needed to establish the efficacy of ketamine infusion and to determine optimal dosing, which may be patient-specific.

CONFLICT OF INTEREST STATEMENT

Natasha M. Archer received clinical trial fees from Global Blood Therapeutics for a clinical trial outside the scope of this work. Matthew M. Heeney is a consultant for Vertex/CRISPR Therapeutics, Novartis, AstraZeneca, Cyclerion, and Micelle Biopharma, and has received Clinical Trial support from Novartis, AstraZeneca, Cyclerion, and Micelle Biopharma. The remaining authors have no conflicts of interest to disclose. The National Institute of Diabetes and Digestive and Kidney Diseases did not participate in the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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