ADJUVANT LOW-DOSE KETAMINE FOR PEDIATRIC SICKLE CELL VASO-OCCLUSIVE EPISODES IN THE EMERGENCY DEPARTMENT

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Abbreviations:

BCHO	University of California San Francisco Benioff Children's Hospital Oakland
ED	Emergency department
LDK	Low-dose ketamine
LOS	Length of stay
NMDA	N-methyl-D-aspartate
NSAID	Non-steroidal anti-inflammatory drug
SCD	Sickle cell disease
VOE	Vaso-occlusive episode

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ABSTRACT

Background: Sickle cell disease (SCD) vaso-occlusive episodes (VOEs) are managed primarily with opioids that can lead to dependence and tachyphylaxis. Ketamine mitigates opioid tolerance and appears efficacious for all-cause pain in the adult emergency department (ED). We hypothesized that ED treatment with low-dose adjuvant ketamine (LDK) for acute VOE is safe and decreases opioid usage in children and young adults with SCD. **Procedure:** In this exploratory study, patients with SCD aged 10-25 years presenting to UCSF Benioff Children's Hospital Oakland ED with VOE were eligible for a single 0.2 mg/kg IV dose of LDK, after receipt of the first IV opioid dose. Safety, tolerability, and subjective experience were assessed prospectively. Pain scores, length of stay, likelihood of discharge from the ED, time to 50% pain reduction, and morphine equivalent usage (mg/kg/h) for the intervention visits were compared to the patient's historical data within the year prior. **Results**: No serious treatment emergent adverse events occurred in the 62 enrolled patient-encounters in 25 individual patients. LDK decreased morphine equivalent usage by 0.06 mg/kg/h (15%; 95% CI [2.3%, 28%], p=0.004), but did not affect pain scores on discharge, time to or likelihood of 50% pain reduction, or likelihood of discharge. Subjectively, when assessed in their first LDK encounter, the majority of patients reported faster pain relief (60%) and desired LDK in the future (68%). **Conclusions**: LDK for SCD VOE in the pediatric ED is safe, subjectively improves the experience of pain, and decreases opioid usage. Larger studies are needed to confirm these findings.

INTRODUCTION

Sickle cell disease (SCD) is caused by a point mutation in the beta-hemoglobin chain that causes the red blood cell to assume a "sickled" morphology under hypoxic conditions such as cellular stress. Vaso-occlusive episodes (VOEs) in SCD are due to microcirculatory inflammatory and thrombotic events in association with altered rheology that lead to ischemia and pain. VOEs remain the most common reason for patients with SCD to be hospitalized.[1,2] Historically, VOEs have been managed with opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and IV hydration.[1,2] Unfortunately there has been little change in VOE management over the last three decades with limited effective non-opioid pain management tools.[3]

Opioid medications have a narrow therapeutic window and patients with chronic pain can develop both tolerance and hyperalgesia, which are postulated to be N-methyl-D-aspartate (NMDA)-receptor mediated processes via activation of the nociceptive system.[4] Hyperalgesia manifests as a heightened sensitivity to pain and increasing symptom severity, while tolerance manifests as increasing opioid requirements for similar symptom control with resulting increase in side effects. As a NMDA receptor antagonist, ketamine is postulated to mitigate this activation.[5] When administered as an IV infusion, ketamine is efficacious in reducing post-operative, chronic, and cancer-related pain, and has emerging utility in all-cause pediatric pain in hospitalized children.[6-8] In adults, IV boluses of ketamine as an adjuvant to opioids have been shown to reduce time to pain control and opioid use in the emergency department (ED) setting. [9-12] Case reports and case series have shown that low dose ketamine infusions have utility in pain reduction in opioid-refractory pediatric and adult patients with SCD.[6,13-16] Ketamine IV bolus as an adjuvant to opioids appears safe in adults presenting to the ED.[17] Additionally,

LDK does not appear to raise blood pressure, which is of particular importance to patients with SCD given their underlying vasculopathy and increased risk for stroke.[18-22] We therefore hypothesized that LDK at 0.2 mg/kg used as an adjuvant to IV opioids in the management of SCD VOE pain in the pediatric ED would be safe, would be well tolerated, and would potentially decrease opioid usage.

METHODS

Prospective patient enrollment occurred at the UCSF Benioff Children's Hospital (BCHO) ED between June 2016 and March 2018. Study enrollment started after approval by the BCHO IRB. The study design was an unblinded, non-placebo controlled, historical control study, within which patients' LDK encounters were compared to their historical visits given the significant inter-patient variability in VOE pain presentation and response. All patients 10 to 25 years of age with SCD and VOE presenting for associated pain were potentially eligible. Exclusion criteria included prior serious adverse event (defined as a cardiorespiratory event requiring intervention), allergic reaction, or emergence reaction with prior exposure to LDK. Patients $\geq$ 18 years were consented, while parents of children <18 years were consented and patients were assented. All patients received the standard of care per our ED SCD VOE protocol and their applicable individual pain plans, including NSAIDs, IV hydration, and intranasal (if applicable) and IV opioids. A planned sample size of 90 was calculated based on a difference in opioid usage of 30% per an adult ketamine study in the ED for all-cause pain with an alpha of 0.05 and beta of 0.2.[9]

Prior to the second dose of IV opioids, consenting patients were given an IV infusion of LDK at a dose of 0.2 mg/kg with no maximum dose. This dose was infused at a rate of 5 mcg/kg/min to minimize psychoactive effects. After LDK, patients were given further doses of IV opioids per our ED standard of care protocol as required for pain control. Our standard of care includes assessment of change in patient pain and need for additional therapy within 30 minutes of receipt of IV opioids. The decision of whether to give additional doses is based on discussion between the provider and the patient and family. After three IV doses of opioids, patient disposition from the ED is determined by the need for ongoing IV pain control as assessed by the patient, family and provider, or based on additional indications (e.g., acute chest syndrome). Patients and families (based on patient age), were given a survey to fill out after receipt of LDK. The survey questions based on a 5-point Likert scale included: 1) if LDK more quickly and more completely relieved pain; 2) if they desired to receive LDK again with future ED visits; and 3) if they experienced nausea/vomiting, a "dream-like" sensation, or symptoms of emergence phenomenon during its infusion. To ensure capture of any emergence-like event, symptoms of an emergence phenomenon included self or parent or nursing report of fear or anxiety during receipt of LDK. All physician and nursing notes during the ED encounter were also reviewed to ensure that no side effects not self-reported on the survey were missed. Patients were allowed to re-enroll 4 weeks after a VOE presentation in which they received LDK, which was considered a separate VOE per the literature.[1]

Chart review was performed on all enrolled patients to a maximum of three prior consecutive historical encounters within the year of the LDK encounter. Patient age, sex, sickle cell genotype, pain score on presentation and discharge, length of stay in the ED, whether the patient obtained 50% pain reduction and if so in what time in minutes, the total opioid usage in

morphine equivalent mg/kg/h, and if the patient was discharged or admitted, were recorded. An average of continuous variables (e.g., morphine equivalent usage) was then calculated. For the LDK visit, the incidence of serious treatment emergent adverse events (defined as a cardiorespiratory event requiring any intervention), the above adverse events, and survey questions were recorded. The historical data were then compared to the LDK visit to investigate the hypothesis.

Data analysis was performed using STATA (StataCorp 2017, Stata Statistical Software: Release 15, College Station, TX). Non-normally distributed continuous variables and dichotomous variables (e.g., discharge or not) were compared using a Wilcoxon sign-rank test. Though not normally distributed, an estimated effect size was estimated using paired student's t-test. A $p < 0.05$ was considered statistically significant.

RESULTS

There were 62 patient encounters representing 25 individual patients enrolled (Table 1). The majority of patients were female (64%) and most had HBSS disease. LDK was tolerated without any serious anticipated or unanticipated treatment emergent adverse event (Table 2). A small percentage of patient encounters experienced nausea without vomiting or emergence or emergence-like symptoms; however, sub-dissociative symptoms that we queried as a "dream-like" or "de-realized" sensation were common. All such events were brief and did not require any medical (i.e., benzodiazepines) or other intervention. A small percentage of patients experienced other, self-reported side effects such as dizziness and blurry vision. Subjectively, a

majority of patients at the time of their first LDK encounter agreed or strongly agreed that LDK more quickly relieved their pain and desired to receive it in the future, while a minority agreed or strongly agreed that it more completely relieved their pain (Table 3). These results were unchanged when comparing subjective data from all encounters.

When comparing the averaged ED encounter(s) with LDK infusion to averaged individual patient historical visits within the prior year, there was a statistically significant decrease in morphine equivalent usage and increase in length of stay (LOS) (Table 4). There was an average comparison of 1.8 historical ED encounters in the prior year to the LDK encounter. There was no difference between the LDK encounters and historical ED encounters in regards to pain scores on presentation or discharge (Supplemental Table 1), likelihood of or time to 50% pain reduction (Table 4 and Supplemental Table 2), or likelihood of discharge from the ED (Supplemental Table 2).

DISCUSSION

We demonstrated that LDK as an adjuvant to IV opioids was safe and well tolerated in our 25 pediatric and young adult patients with SCD presenting to the pediatric ED for VOE related pain. No patient had a serious side effect requiring intervention though incidence of sub-dissociative or a “dream-like” feeling was common. Notably, LDK encounters had a significant decrease in morphine equivalent usage when compared with individual historical control data. Subjectively the majority of patients when surveyed during their first pain encounter felt that LDK in

conjunction with IV opioids provided faster pain relief and desired to receive it again. Length of stay increased, likely due in part to LDK being given as an infusion (0.2 mg/kg given at 5 mcg/kg/min, or 40 min) in order to minimize the dissociative effects. Pain scores and likelihood of discharge from the ED were unchanged when comparing individual patient LDK encounters with historical ED encounters.

Four case series have shown low dose ketamine infusion at a dose of 0.05-0.25 mg/kg/h [0.8-4.2 mcg/kg/min]) to be safe for pediatric inpatients with SCD. [6,13,14,16] Five of 119 pediatric and young adult patients in these studies discontinued ketamine, four from dysphoria and one from hypertension and unresponsiveness. For these prior studied patients, there was no change in pain scores or opioid utilization with the addition of low dose ketamine infusion. In the ED setting, there is only the recent 2018 publication by Lubega et al. [18], which studied 240 Nigerian pediatric patients with SCD and acute pain secondary to VOE, randomizing them to single dose morphine 0.1 mg/kg versus LDK 1.0 mg/kg. Although they were able to show non-inferiority of LDK to morphine, it is difficult to extrapolate to our setting based on population differences and significant difference in dose, which led to a much higher rate of transient LDK-related side effects.[18] Population differences would assume higher rates of opioid tolerance in patients with SCD in high-income settings, thus the potential synergistic benefit of LDK with morphine rather than utilization of one versus the other in the ED setting.

Patients with SCD face both acute pain during VOEs and also the burden of chronic pain and associated tolerance and hyperalgesia that develops in 30-40% of patients.[23] The current standard of care for acute pain episodes revolves around IV opioids per guidelines published by the National Heart, Lung, and Blood Institute at the National Institute of Health and recently updated by the American Society of Hematology (ASH).[1,24] The ASH guidelines make

conditional recommendations (based on very low certainty of evidence) for use of NSAIDs for 5-7 days as well as LDK infusion in the inpatient setting.[24] However, ancillary medications such as NSAIDs, while opioid-sparing, have shown inconsistent results in improving pediatric SCD pain, while having significant gastrointestinal and renal side effects.[25-27] No recommendation is made regarding LDK in the ED setting due to lack of evidence to date.

Similar to prior pediatric SCD pain studies, we allowed patients to enroll more than once onto the study and compared patients to themselves given the significant inter-patient variability in pain presentation and response. In order to prevent bias from those patients who re-enrolled, survey data were based on the first LDK encounter though results were unchanged when compared across the 62 LDK encounters. Our study was limited by the number of unique patients and patient encounters enrolled as well as the lack of a blinded, placebo-controlled design allowing for potential placebo-effect of a novel agent. Given the number of median encounters was two (interquartile range 1,3), it is possible that some of this placebo-effect may have been decreased in the subsequent encounter. The lack of change in survey data across all encounters compared to the first patient encounter also argues against a placebo-effect in the first encounter. Additionally, given the nature of chronic SCD-related pain, it was not surprising that the median patient age was 19 years. Still, with an interquartile range of 14-22 years, this study remains somewhat generalizable to younger patients with SCD.

Overall, our study demonstrates that LDK was tolerable at a dose of 0.2 mg/kg IV in the pediatric ED setting with a significant opioid sparing effect when comparing patients to their unique historical ED encounters. Future studies should be performed to verify the safety as well as subjective and objective benefit of LDK, especially in terms of opioid-sparing effect. Additionally, different doses and infusion rates may also be tolerable, minimizing the LOS

increase we saw and also allowing for more rapid administration of additional pain control medications. LDK appears to be a useful adjunct to the existing standard of care in the ED setting for pediatric and young adult patients with SCD and VOE, especially given the limited options for non-opioid pain management.

CONFLICT OF INTEREST STATEMENT

There are no relevant conflicts of interest for any author

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