

# Low dose ketamine infusion for pediatric hematology/oncology patients: case series and literature review

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## Abstract

**Background:** Management of refractory pain in pediatric sickle cell disease (SCD) and oncology is reliant on opioids though high opioid dosing increases side effects and tachyphylaxis. We introduced low dose ketamine infusion (LDKI) to our inpatient unit to determine if LDKI was safe and tolerable. We subsequently hypothesized that LDKI would improve pain scores but not decrease opioid utilization. **Procedure:** We retrospectively reviewed inpatients from LDKI initiation in March 2014 through October 2017, analyzing each patient's first admission with LDKI. The day prior to LDKI initiation was compared with the day of LDKI initiation and two subsequent days in regard to cumulative daily opioid utilization, vital signs and pain scores. For patients with SCD, the LDKI admission was compared with up to three admissions in the prior year for a vaso-occlusive event. **Results:** Nineteen patients (12 oncology, 7 SCD) with a median age of 14.6 years received LDKI for a median of 6 days at a median initial dose of 0.06 mg/kg/h (1.1 mcg/kg/min). There was no change in pain scores, heart rate or opioid utilization when comparing the day prior to LDKI initiation with subsequent days. No patient discontinued LDKI due to intolerance. For patients with SCD, there was a median 32% reduction in cumulative pain scores when comparing the LDKI admission with prior admissions. **Conclusions:** LDKI is well tolerated and may be a viable option for refractory pediatric cancer- and sickle cell-related pain. Future study is required to further delineate appropriate dosing and patients most likely to benefit.

## INTRODUCTION

The management of pain in patients with sickle cell disease remains incomplete and heavily reliant on opioid therapy. [1] Similarly, pediatric oncology patients with refractory pain due to severe mucositis, bone pain due to tumor or metastases and end of life pain have limited utilized treatment options beyond opioids. [2] For accredited hospitals, The Joint Commission requires pain management standards inclusive of assessment of pain interventions with the goal of improving quality of care and decreasing adverse effects of opioid usage, especially with increasing dosages. [3] High opioid doses for intractable cancer pain and chronic sickle cell related pain are often ineffective and should be avoided due to tachyphylaxis and increasing side effects including sedation, constipation, respiratory depression, hyperalgesia, allodynia, myotonia and seizure. [4-6]

Chronic opioid utilization leads to tolerance due to downregulation of N-methyl-D-aspartate (NMDA) receptors in the spinal cord. [7] As a NMDA receptor antagonist, ketamine may have beneficial effect on opioid tolerance and hyperalgesia and act synergistically with morphine. [4,7] Ketamine additionally has antidepressive effects through its NMDA receptor blockade. [8] Ketamine is rapidly metabolized and highly bioavailable when given intravenous or intramuscular. [8] Multiple publications have reported utilization of subanesthetic continuous infusion ketamine (i.e., [?]1 mg/kg/h) in pediatric sickle cell, oncology and chronic pain patients at doses ranging from 0.02-0.4 mg/kg/h (Table 1). [4, 9-23] These studies while generally retrospective have shown low dose ketamine infusion to be well tolerated with subjective benefit in some patients without overall impact on opioid utilization. Based on this literature, we developed a quality improvement initiative to introduce low dose ketamine infusion (LDKI) to our hematology/oncology inpatient

unit. We subsequently aimed to determine if LDKI was safe and tolerable in our population and hypothesized that LDKI would improve pain scores but not decrease opioid utilization. Here we review our institutional experience and the relevant literature to date.

## METHODS

We designed a protocol as a quality improvement initiative for introduction of LDKI for refractory or chronic pain (Supporting information) in 2014 for our pediatric and young adult hematology and oncology patients at UCSF Benioff Children’s Hospital Oakland. Protocol development occurred with involvement of the pain anesthesiologist, palliative care team, hematology/oncology, nursing and pharmacy to provide LDKI at a dose of 1-10 mcg/kg/min (0.06-0.6 mg/kg/h), with patients generally being prescribed 1-5 mcg/kg/min unless with chronic refractory pain or at end of life (Supplemental material). We subsequently obtained institutional review board (IRB) approval to retrospectively review our initial experience from protocol initiation in March 2014 through October 2017, when IRB approval was obtained for hematology/oncology patients through age 21 years prescribed LDKI. Patients were included during their first admission with LDKI. There were no exclusion criteria.

For these patients, their primary diagnosis and reason for admission were recorded in addition to all concomitant scheduled and as-needed medications (opioid and non-opioid) with a focus on use on benzodiazepines for LDKI side effects. Cumulative daily (24 hour) opioid doses were converted to morphine equivalents. Vital signs and pain scores from up to five days before and after initiation of LDKI were recorded and averaged in 24-hour increments. The day of initiation of LDKI was designated day 0 and compared with the day prior to LDKI initiation as well as day 1 and 2 after LDKI initiation to determine if there was a significant daily decrease in opioid utilization, pain scores or heart rate. Given the inter-patient variability and the fact that most all patients with sickle cell disease (SCD) were initiated on LDKI at time of admission, these patients were compared with prior admissions for a vaso-occlusive event (VOE), with a maximum of three admissions recorded within one year prior to the admission in which they received LDKI. These admissions were reviewed to determine if there was a significant decrease in pain scores, opioid utilization or hospital length of stay in the LDKI admission as compared with the prior admissions. Daily physician and nursing progress notes were reviewed for subjective descriptions of each patient’s pain and any reported side effects to ketamine. Given the small sample size, data were compared using medians and Mann Whitney U testing. Friedman test for repeated measures was utilized when there were repeated days with the same number of data points.

## RESULTS

Nineteen patients (12 oncology, 7 sickle cell) with a median age of 14.6 years received LDKI for a median of 6 days at a median initial dose of 0.06 mg/kg/h (1.1 mcg/kg/min) (Table 2). Patients with SCD were all admitted for a VOE and only 2 of the 7 were on opioids (for 1 and 3 days) prior to initiation of LDKI. The other 5 patients were initiated on LDKI on the day of admission with opioids. For patients with both sickle cell disease and cancer, there was no significant change in pain scores, heart rate or opioid utilization when comparing the day prior to LDKI initiation (for oncology patients), the day of LDKI initiation, and the two subsequent days after LDKI initiation (Table 3). No patient developed hypertension or discontinued the LDKI due to intolerability. Four patients had a single side effect each including two with dream-like feeling (dysphoria) and one each with blurry vision and drowsiness, one of which required LDKI dose reduction and none of which were treated with benzodiazepines. For patients with SCD, comparing the LDKI admission with prior admissions did not show a significant difference in pain scores, opioid utilization or hospital length of stay though there was a median 32% reduction in pain scores when comparing the entire admission with LDKI to the prior admissions (Table 4).

## DISCUSSION

Similar to prior publications in pediatric hematology/oncology patients, we were able to show that patients initiated on LDKI tolerated the infusion without significant side effects resulting in LDKI discontinuation. Patients utilized LDKI for a median of 6 days (IQR 4, 11) also signifying tolerability. Also similar to prior

publications, LDKI did not impact opioid utilization. Although we did not show that there was a significant impact on pain scores, there may have been a clinically meaningful, subjective reduction in pain. Overall, there was a 30% reduction in median pain scores when comparing the entire cohort on the day of LDKI initiation (day 0) and the subsequent day (day 1). Similarly, when comparing patients with sickle cell disease receiving LDKI to prior admissions without LDKI, there was a 32% reduction in median pain scores, though this was underpowered to reach significance.

Studies attempting to define clinically meaningful pain reduction are limited. Generally, a 30%-50% decrement in pain scores is considered clinically meaningful, though cannot be generalized to the individual patient. [24] In studies in both acute, post-operative pain as well as chronic pain, a decrement in the visual analog scale of 20% corresponded to minimal improvement, while 30%-35% decrement corresponded to much improvement. [25-26] Myrvik et al. [27] note in a small pediatric SCD cohort that a decrement in the visual analog scale of 0.97 cm and 0.9 in the numeric rating scale was the minimum clinically significant improvement. Numerical pain rating scales are limited due to being a unidimensional assessment of pain at one moment in time in patient cohorts with dissimilar pain tolerance and medication response. [28] As noted by Nobrega et al. [18] in their study of pediatric patients with sickle cell disease, there are significant inter-patient differences in response to LDKI; therefore, there may be a subset of patients more likely to benefit but not yet clearly delineated.

Prior studies with LDKI in pediatric hematology/oncology patients (Table 1) have similarly struggled to define an objective response for multiple reasons: 1) studies were almost all retrospective; 2) patients with end-stage cancer had increasing pain due to their underlying condition; 3) patients' pain may have naturally improved over time and improvement unnecessarily attributed to LDKI initiation (i.e., regression to the mean); 4) multiple different measures were utilized to define which pre-LDKI and post-LDKI pain scores to compare; and 5) challenges of generalizing an intervention with significant inter-patient variability. The single recent multicenter prospective observational trial by Courade et al. [9] in pediatric and young adult cancer patients reported meaningful benefit in pain scores when comparing the day of LDKI initiation and two days later. Given the rapid onset of action of LDKI, two days may or may not be an appropriate time frame to measure response. More important though, 47% of patients found LDKI to be "very helpful," which further argues that the objective response was real, at least for some of the patients. Nobrega et al. [18] reported a meaningful reduction in pain scores in a large cohort of pediatric patients with sickle cell disease, but this was comparing baseline pain scores with pain scores taken after LDKI discontinuation, which was several days later and could be attributed to the natural improvement in patient symptoms. The two retrospective studies of patients with chronic pain reported improvement in pain scores immediately following LDKI which is the more pathophysiological expected time frame for response given the rapid onset of action of LDKI. [22,23]

Additionally, the best dose of LDKI is yet to be defined. In our protocol we set a dose range of 1-10 mcg/kg/min (0.06-0.6 mg/kg/h) which is similar to the doses used in the majority of the other reported pediatric studies. Given we reviewed patients after protocol initiation, the majority of patients were started on the low end of the dose range given the median dose of LDKI was 0.06 mg/kg/h (1 mcg/kg/min). Whether patients may have had a more meaningful response at higher doses is not clearly delineated by our or other studies. The single patient that required dose reduction in our retrospective analysis was on 2 mcg/kg/min (0.12 mg/kg/h) and reduced to 1 mcg/kg/min (0.06 mg/kg/h). Coubarde et al. [9] similarly note that patients with side effects were all on lower doses (<0.05 mg/kg/h). Our study has multiple limitations including: 1) being a retrospective analysis; 2) having a small, heterogenous cohort and 3) lacking an *a priori* definition of best pain scores to compare and what entails a clinically meaningful result.

Since initiation of our LDKI protocol, empirically we have seen that certain patients with sickle cell disease and chronic pain perceive benefit with LDKI while others do not, not dissimilar to certain patients who prefer hydromorphone to morphine and vice versa. We have also empirically seen that many patients with chronic pain and at end of life are maintained on higher doses (i.e., 3-10 mcg/kg/min, 0.18-0.6 mg/kg/h). Understandably, some patients may be benefiting due to a placebo effect especially with the use of a "new"

intervention. Yet, overall, unlike adult patients who may not tolerate LDKI well leading to lack of consensus on benefit, the limited studies in pediatric patients do not show high rates of side effects leading to intolerability or discontinuation, parallel to what we show here. [29-31] Thus, similar to the conclusion of Bredlau et al. [31], we believe that LDKI is well tolerated and may be a viable option for refractory pediatric cancer- and chronic sickle cell-related pain and therefore should be offered routinely for these indications and assessed for benefit. Future study is required to further delineate appropriate dosing and the pediatric hematology/oncology patients most likely to benefit as well as to explore utilizing LDKI in the outpatient setting.

## CONFLICT OF INTEREST STATEMENT

There are no relevant conflicts of interest for any author

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**Supporting Material:** Ketamine infusion management protocol

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