Clinical pain research

Felix Anthony Lubega*, Mithrika S. DeSilva, Deogratias Munube, Rita Nkwine, Janat Tumukunde, Peter K. Agaba, Mary T. Nabukenya, Fred Bulamba and Tonny S. Luggya

Low dose ketamine versus morphine for acute severe vaso occlusive pain in children: a randomized controlled trial

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Abstract

Background and aims: Acute pain episodes associated with sickle cell disease (SCD) are very difficult to manage effectively. Opioid tolerance and side effects have been major roadblocks in our ability to provide these patients with adequate pain relief. Ketamine is cheap, widely safe, readily available drug, with analgesic effects at sub-anesthetic doses and has been used in wide range of surgeries, pediatric burns dressing change and cancer related pain however, literature concerning its use in sickle cell crises is still limited in our setting. This study aimed to establish if 1 mg/kg of intravenous ketamine is non inferior to intravenous morphine 0.1 mg/kg in severe SCD-associated pain.
Methods: We performed an institutional review board-approved randomized, prospective, double-blinded, active-control, non-inferiority trial at the national referral sickle cell center. Children between 7 and 18 years of age with severe painful sickle cell crisis, defined by numerical rating scale score of greater or equal to 7 were enrolled. Patients were consented and randomized to receive, either IV ketamine (LDK) 1 mg/kg or IV morphine (MOR) 0.1 mg/kg as an infusion over 10 min. The primary endpoint is maximal change in Numerical Rating Scale (NRS) pain score. Secondary outcomes were, incidence of adverse effects, optimal time to and duration of action of ketamine and incidence of treatment failures by treatment group. A clinically meaningful difference in validated pain scores was defined as 1.3 units. Assuming both treatments are on average equal, a sample size of 240 patients (120 per group) provided 95% power to demonstrate that IV LDK is non-inferior to IV morphine with a 0.05 level of significance and a 10% non-inferiority margin. All analyses were based on a modified intention to treat. This trial was registered with clinicaltrials.gov NCT02434939.
Results: Two hundred and forty patients were enrolled (LDK120, MOR120). Demographic variables and baseline NRS scores (8.9 vs. 9.2) were similar. LDK was comparable to MOR in the maximum change in NRS scores, 66.4% vs. 61.3% (MD 5.5; 95% CI –2.2 to –13.2). Time to achieve maximum reduction in NRS pain scores was at 19.8 min for LDK and 34.1 min for MOR. The average duration of action for LDK was 60 min. MOR had more patients still at maximum effect at 120 min (45.8% vs. 37.5%; RR 1.2; 95% CI 0.9–1.7). LDK patients were 11.3 times more likely to develop side effects, though were transient, anticipated and non-life threatening (37.5% vs. 3.3%). MOR had significantly more treatment failures 40% vs. 28.3% (RR 0.7; 95% CI 0.5–1.03, $p = 0.07$) Vital signs and sedation scores were similar in both groups.
Conclusions: Intravenous LDK at 1 mg/kg provides comparable analgesic effectiveness as IV MOR in the acute treatment of severe painful sickle cell crisis in children in the day care sickle cell center. However, it is associated with a high incidence of several transient, non-life threatening mild side effects.
Implications: Intravenous ketamine at 1 mg/kg can be a reliable alternative to morphine in the management of severe painful sickle cell crisis especially in a resource limited area where morphine is not readily available.

Keywords: low dose ketamine; vaso-occlusive crisis; morphine; sickle cell disease.

***Corresponding author: Felix Anthony Lubega,** Department of Anaesthesia and Critical Care, Aga Khan University Hospital Nairobi, P. O. Box 30270-00100, Nairobi, Kenya, E-mail: felix.lubega@aku.edu
Mithrika S. DeSilva: Department of Paediatrics, University of Sydney, Sydney, Australia
Deogratias Munube: Sickle Cell Clinic, Department of Paediatrics and Child Health, Mulago National Referral Hospital, Kampala, Uganda
Rita Nkwine, Janat Tumukunde, Peter K. Agaba, Mary T. Nabukenya and Tonny S. Luggya: Department of Anaesthesia and Critical Care, College of Health Sciences, Makerere University, Kampala, Uganda
Fred Bulamba: Department of Anesthesia, CURE Children's Hospital of Uganda, Mbale, Uganda

1 Introduction

Painful vaso-occlusive crisis (VOC) is the hallmark of sickle cell disease (SCD) with an unpredictable onset that varies in frequency and intensity [1–4]. It accounts for 90% of sickler's admission into the day care centre with eventual hospital admission. Of these, 70% are associated with refractory pain that is often undertreated [5, 6] and has been associated with increased morbidity and mortality [7–10].

Opioids are the mainstay therapy for management of severe sickle cell related pain [11, 12]. They mediate analgesia via mu receptor activation with consequent presynaptic inhibition of substance P release. Chronic opioid exposure in patients with SCD plays an important role in the development of refractory pain [13, 14]. This is thought to be modulated via the abnormal activation of N-methyl D-aspartate (NMDA) receptor in the central nervous system and long term potentiation of synapses between nociceptive C fibers and neurons in the spinal cord resulting in hyperalgesia and opioid tolerance [15–17].

Other associated side effects of opioid use are respiratory depression and possible addiction. Morphine, the commonly used opioid has a long time to maximal pain reduction effect resulting in suboptimal pain control during a crisis. It is not readily available in low resource settings creating a need to explore other options which offer equally good analgesia with low cost and a better safety profile [18, 19].

Ketamine is a non-competitive NMDA receptor antagonist that has been shown to modulate opioid tolerance and opioid induced hyperalgesia in the following groups, i.e. animal models [20, 21], refractory SCD-related pain [22–25] and cancer related pain [26–28]. Ketamine exhibits anti inflammatory properties [29, 30] and has a very large therapeutic window [31–34].

The use of ketamine in acute management of VOC has been limited to small retrospective case series utilizing it as an adjunct to opioid therapy [23, 24, 34, 35]. Caitlin in the largest retrospective case series of 33 children and adolescents found, that low dose ketamine lacked an opioid sparing effect with patients receiving ketamine reporting higher scores and higher opioid usage compared to those without ketamine (6.48 vs. 5.99; $p = 0.002$ and 0.040 mg/kg/h. vs. 0.032 mg/kg/h; $p = 0.004$, respectively) [34]. This however was related to the low doses of ketamine utilized.

The aim of the study was to compare maximal pain reduction of ketamine to morphine as measured by the Numerical Rating Scale (NRS). In addition, we evaluated time to maximal analgesic effect, duration of action, incidence of treatment failure and side effects of either intervention reported within 120 min of study period.

2 Materials and methods

2.1 Study design and setting

This study was approved by the Makerere University, School of Medicine Research and Ethics Committee (SOMREC) and was registered to the clinical trials.gov Registry with identifier number NCT02434939. This was a prospective, randomized, double-blind, active-controlled non-inferiority trial conducted from June 2015 to February 2016 at Mulago National Referral and Teaching Hospital (MNRTH) in Uganda, which has a 1500 bed capacity and receives on average 48,000 patients annually at its Accident and Emergency (A&E). The sickle cell day care treats 10,000 patients annually with VOC accounting for 80–90% of these.

2.2 Eligibility

All children with SCD aged 7–18 years with severe acute painful crisis were eligible for recruitment. We excluded those with oxygen saturation less than 90%, systolic blood pressure less than 90 mmHg or greater than 180 mmHg, pulse rate less than 50 or greater than 120 beats/min, respiratory rate less than 10 or greater than 30 respirations/min, altered mental status, current enrolment in another clinical drug trial, history of a stroke, increased intra cranial pressure, glaucoma and failed/difficult intravenous access. Parental consent and child assent for children above 8 years was obtained from all participants.

2.3 Sample size

Power analysis determined that a sample size of at least 120 subjects per group would achieve 95% power to detect a 10% change in NRS scores between treatment groups, with estimated group SDs of 2.3 for a 2-sided test with a significance level α of 0.05.

2.4 Randomization and concealment

Block randomization with a block of 10 used to randomly assign participants to either receive ketamine or morphine in equal numbers for the two groups. A computer program was used to generate the randomization sequence by an independent statistician.

The ketamine group received intravenous ketamine (1 mg/kg) and the morphine group received intravenous

morphine (0.1 mg/kg) and blinding of both participants and study investigators was achieved by use of 20 mL syringes of similar appearance and consistency. The drugs were mixed by the study pharmacist (on site) patient per patient according to allocation. The mixed drug was labeled with the patient study number and delivered to the research assistant in a transparent syringe (all drugs are colorless liquids).

Concealment was achieved by making sure that each syringe was labeled according to sequence-generated codes earlier presented as a list of sequential random treatment codes. The labeled syringes were brought in an opaque carrier envelope to the clinic and handed to the attending nurse who retrieved them with their sticker code number, similar to computer generated number sequence, becoming the patients study number.

2.5 Outcome measures

Our primary outcome measurement was the maximum change on the verbal NRS pain scale as a percentage of their initial score (baseline). Maximal change in NRS pain score is to be defined as the largest change from patient's baseline pain score. The NRS was used to measure a patient's subjective level of pain on a scale from 0 (representing no pain at all) to 10 (the worst pain imaginable) using whole numbers. The NRS score was documented just prior to the administration of the study drug (time zero). After infusion of the study drug was complete, NRS scores were documented at 5, 10, 20 and then every 20 min thereafter up to 120 min. We stopped recording NRS scores prior to 120 min if the patient requested a third dose of the study drug, withdrew consent or developed a severe adverse effect.

Secondary outcome measures:

- **Time to maximal analgesic effect and duration of action of ketamine**
  Following dosage with study medication, the amount of time taken to demonstrate the maximal change in the patient's NRS pain score. Duration of maximal change is how long the patient's pain score remained at this level.
- **Incidence of side effects, including outlying vital signs**
  The patient will be assessed for vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation), Ramsay Sedation Scale (RSS) score at 5, 10, 20 min following medication administration and then every 20 min until a total of 120 min from the first dose of study medication, outlying vital signs recorded (systolic blood pressure less than 90 mmHg or greater than 150 mmHg, Heart rate less than 50 bpm or greater than 150 bpm, oxygen saturation below 90%, respiratory rate below 9 breaths/min or greater than 40 breaths/min and RSS of 1 or greater than 3). The RSS was used to assess the level of agitation or sedation caused by the intervention. The scale ranges from 1 (anxious/agitated) to 6 (no response to stimulus-deep sedation) with 2 being the optimal (cooperative, oriented and tranquil). A checklist for side effects like airway problems, allergic reactions, salivation, dysphoria, nystagmus, respiratory/cardiac arrest, awakening hallucinations, nausea/vomiting was used.
- **Incidence of treatment failure by treatment group**
  Requiring more than two doses of the study medication provided for adequate pain control.

2.6 Study procedures

The patient's weight (kg) was taken and recorded with a standardized calibrated weighing scale (SECA 762 calibrated to one decimal point).

Baseline clinical parameters which include pulse rate (PR), respiratory rate (RR), blood pressure (BP), temperature (Temp.), oxygen saturation (SpO_2), level of consciousness (GCS), Numerical Rating Scale Pain scores (NRS), and sites of VOC pain were noted. A peripheral intravenous cannula, G22-G20 was placed with fluid load of 15 mL per kg of a crystalloid solution (normal saline or ringers lactate), repeated if required (persistent evidence of dehydration). All other non-analgesic therapies were administered concurrently with the study interventions according to the management protocols of the sickle cell clinic.

After receiving the bolus of fluid, the research assistant retrieved an envelope from the pharmacist, picked the randomization number which he wrote on the patient's clinical research form. The envelope contained the assigned medication in a 20 mL luer lock syringe which was then diluted to 15 mL with normal saline before administering it to the patient over 10 min through a Braun Perfusor IV infusion syringe pump.

The vital signs (BP, PR, SpO_2, RR) NRS and Ramsay Sedation Scores (RSS) were reassessed and recorded at 5, 10 and 20 min after the end of the drug infusion. At 20 min, patients with NRS of 5 and greater received a second dose of their allocated study drug. If the NRS was less than 5, they would continue to be reassessed every 20 min (vital signs, NRS, RSS and adverse effects) until either inpatient admission to the ward or up to 120 min, after which they

were cared for by the ward team. Patient monitoring was conducted throughout the period the child was in the day care center. If they required a third dose of pain medication at any time during the study, this was deemed as treatment failure and the treating pediatrician was contacted to provide further pain control according to the sickle cell pain management protocol.

Any study drug side effects as listed in the risks and safety section were monitored for among the study subjects and treated by the study team.

2.7 Data management

Interviewer-administered and pre-tested questionnaires were used for data collection. The data was cleaned, coded, and double-entered into Epidata version 3.1, then exported and analyzed with STATA®Version12 (Statacorp LP). Effective analyses was performed with a modified intention to treat. Comparisons was done using *t*-test or Wilcoxon rank sum test depending on distribution of continuous variables, and χ^2 or Fisher's exact test for the categorical variables. In order to assess for time to maximal effect, we constructed Kaplan Meier survival curves. The outcomes were then compared using a log rank test to determine if differences were statistically significant. The relative risks were calculated as the measures of association as well as absolute difference in the outcomes including pain and sedation scores.

3 Results

We screened 800 participants for this study and 560 were excluded while 240 children were enrolled with 120 assigned to one of the two groups (Fig. 1).

Overall, demographic characteristics were similar between the 2 groups as shown in Table 1. The average age of children was 11.8 (3.5) years, with a weight of 30.4 (12.1) and average NRS pain score of 9.1 (1.1) as shown in Table 1.

The primary outcome measured was the maximum percentage reduction in NRS pain score from baseline between the two groups (Table 2) and was comparable in both arms LDK (66.4 ± 29.9) MOR (61.3 ± 28.7) with a *p* value of 0.18.

However, the time to maximal change was significantly shorter in the LDK (19.8 ± 14.4) than in the MOR (34.1 ± 22.1) $p < 0.01$ (Fig. 2).

We reported the NRS scores as a percentage change from baseline over time. In both groups, there was a comparable steady trend of reduced pain over time however,

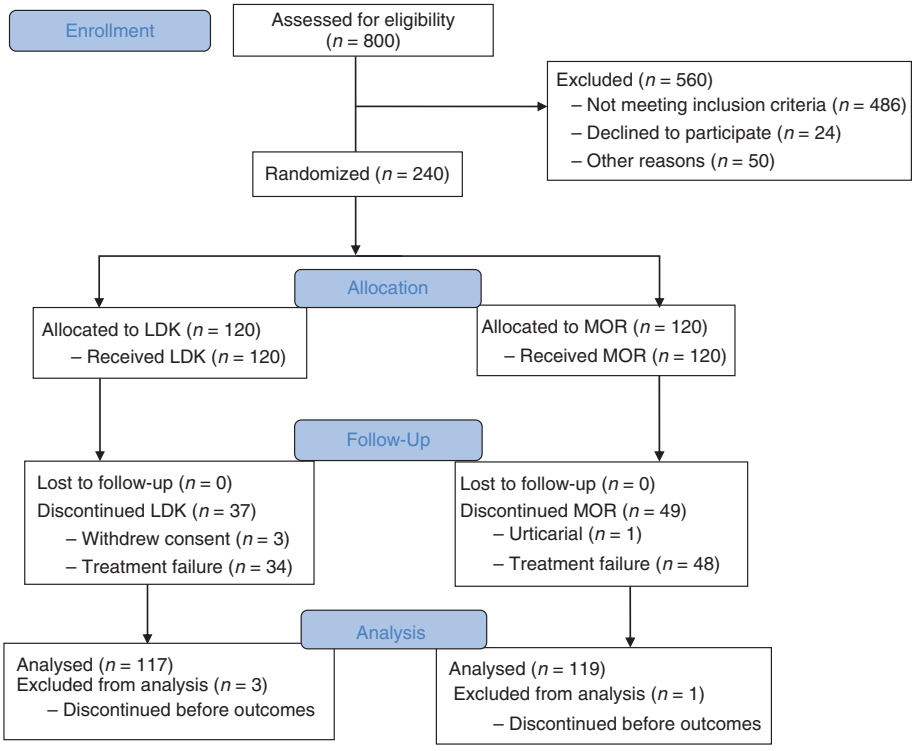

Fig. 1: CONSORT diagram.

Table 1: Baseline characteristics.

Variable	Mean ± SD or *n* (%)		*p*-Value
	LDK (*n* = 120)	MOR (*n* = 120)	
Age (years)	11.8 ± 3.4	11.8 ± 3.6	0.49
Weight (kg)	30.8 ± 11.9	30.0 ± 12.2	0.31
Sex			
Male	43 (35.8)	42 (35.0)	0.89
Female	77 (64.2)	78 (65.0)	
Medication			
Prior med	31 (25.8)	42 (35.0)	0.12
No prior med	89 (74.2)	78 (65.0)	
Characteristics			
NRS pain score	8.9 ± 1.2	9.2 ± 1.0	0.93
Temperature (°C)	36.7 ± 0.86	36.8 ± 0.74	0.94
Systolic BP (mmHg)	113.7 ± 14.0	115.2 ± 15.7	0.78
Diastolic BP (mmHg)	64.7 ± 12.3	65.2 ± 14.1	0.62
Heart rate (bpm)	95.8 ± 15.8	98.8 ± 17.8	0.91
SpO_2	93.9 ± 4.8	94.7 ± 3.4	0.94
Respiratory rate (bpm)	23.8 ± 5.2	24.5 ± 6.4	0.81
GCS	15	15	
HB (g/dL)	7.6 ± 1.4	8.3 ± 5.3	0.90
Site of pain			
Extremity	60 (50)	58 (48.3)	0.3
Back	18 (15)	27 (22.5)	
Chest	30 (25)	23 (19.2)	
Others[a]	12 (10)	12 (10)	
Status			
Discharged	109 (90.0)	108 (89.2)	0.60
Admitted	11 (5.8)	12 (8.3)	

[a]Others represent abdomen head.

differences were noted at 25 and 30 min. In the ketamine group, there was a rapid 25% decrease in pain scores whereas a corresponding increase in the morphine group was noted (Fig. 3).

More patients in the morphine group required more doses: a second dose was administered in 21.4% of the ketamine group vs. 24.4% of the morphine group ($p = 0.07$). A third dose was requested for 40.3% of the morphine arm and 29.1% of the ketamine arm ($p = 0.07$) as shown in Table 2. Patients in the ketamine group were 11.5 times more likely to develop a side effect LDK 45 (37.5%) MOR 4 (3.3%) and were more likely to occur at T5 before clearing by T25 (Table 3). Nystagmus and dysphoria were the commonest side effects with 15% and 11.3%, respectively. No serious or life-threatening adverse events were observed.

One patient in the morphine arm was terminated due to urticaria for fear of a worsened reaction because he required a second dose. Six patients in ketamine arm received atropine for salivation. Eight patients required midazolam for dysphoria persisting past 10 min, otherwise continuous reassurance was the preferred therapy (Table 4).

There was no significant variation in Ramsay Sedation Score from baseline after drug administration in both groups. No differences were found in vital signs between the two groups.

4 Discussion

This study was conducted to assess the role of low dose ketamine as a non-inferior sole-analgesic alternative to morphine in the management of children with SCD presenting with acute severe vaso occlusive crisis (VOC) at Mulago hospital. It is the largest known prospective randomized double-blinded trial comparing the two drugs and the first of its kind to be performed in a pediatric sickle cell population. Most prior studies were retrospective case series where ketamine was employed as an adjunct to opioid therapy [22–25, 34, 35] and differed in the dose and mode of delivery (IM Vs IV) [23, 35–37]. There are however two RCTs done in adult population utilizing ketamine as a sole analgesic in the ED [38, 39].

We used a dose of 1 mg/kg in order to maximize analgesic potential. This was based on Miller's findings that recommended use of a higher dose infused for a longer time to potentially improve the duration of sustained maximal effect which would desirable for managing acute severe VOC.

We found that ketamine (LDK) was comparable to morphine (MOR) in maximal change of NRS pain scores from baseline. An overall change of greater than 50% reduction was observed in both groups. An even higher change of over 75% reduction was realized when the treatment failures were excluded. Our results are similar to earlier studies done [38, 39]. Contrary to our findings, a retrospective case series of 33 children and adolescents found that LDK lacked an opioid sparing effect with patients receiving ketamine reporting higher scores and higher opioid usage compared to those without ketamine. This study however, utilized ketamine at a lower dose (0.1 mg/kg/h) [34]. Our observed differences are best explained by the higher dose of ketamine used (1 mg/kg) and the longer duration of infusion (10 vs. 5 min) utilized in the trial which potentiated the maximal effect observed.

There were significant differences in percent change observed at T25 and T30 between the groups with a rapid 25% decrease in pain scores for LDK whereas a corresponding increase in the morphine group was noted. This was largely due to the fact that more patients in MOR arm

Table 2: Treatment outcomes among patients in the LDK and MOR arms.

Variable	*n* (%) or Mean ± SD				MD (95% CI)	*p*-Value
		LDK		MOR		
Maximum (percentage) change in NRS ± SD						
Overall	117	66.4 ± 29.9	119	61.3 ± 28.7	5.5 (−2.2 to 13.2)	0.18
Excluding treatment failures	83	81.1 ± 18.0	71	79.8 ± 16.9	1.6 (−5.3 to 8.5)	0.54
Among treatment failures	34	33.8 ± 24.2	48	33.9 ± 19.1	0.1 (−4.6 to 20.7)	0.89
Those still at maximum effect at 120	45	80 ± 18.7	55	81.7 ± 17.0	−1.7 (−13.6 to 3.7)	0.42
Time (minutes) to maximum effect						
Overall	117	19.8 ± 14.4	119	34.1 ± 22.1	−14.4 (−19.6 to −9.3)	**<0.001**
Excluding treatment failures	83	20.0 ± 15.1	71	39.4 ± 25.0	−19.4 (−28.3 to −10.8)	**<0.001**
Among treatment failures	34	19.4 ± 12.5	48	25.5 ± 12.1	−6.1 (−16.4 to −3.4)	**0.05**
Those still at maximum effect at 120	45	22.6 ± 15.9	55	42.9 ± 25.3	−20.3 (−25.2 to −15.1)	**<0.001**
Duration (minutes) of max effect ± SD	38	60.0 ± 28.7	16	58.5 ± 30.3	−2.5 (−17.0 to 12.9)	0.47
Mean pain scores at different time periods ± SD						
T5	95	4.5 ± 3.0	120	6.2 ± 2.5	−1.6 (−2.4 to −0.2)	1.00
T10	112	4.1 ± 3.0	120	5.6 ± 2.7	−1.4 (−2.2 to −0.7)	1.00
T20	120	4.5 ± 3.2	120	5.3 ± 2.9	−0.7 (−1.5 to 0.1)	0.97
T25	42	4.5 ± 3.0	73	6.0 ± 2.1	−2.0 (−4.0 to −0.1)	0.99
T30	42	4.8 ± 3.3	73	5.9 ± 2.5	−1.2 (−3.2 to 0.8)	0.96
T40	117	3.8 ± 3.3	119	4.0 ± 2.8	−0.2 (−1.0 to 0.6)	0.69
T45	7	5.3 ± 4.0	3	5.3 ± 1.5	0	0.51
T50	7	4.3 ± 3.5	3	4.7 ± 1.5	0	0.60
T60	83	2.4 ± 2.5	71	2.2 ± 2.0	0 (−0.9 to 0.9)	0.23
T80	74	2.4 ± 2.1	70	2.0 ± 1.7	0.5 (−0.3 to 1.2)	0.10
T100	63	2.4 ± 2.3	64	1.7 ± 1.7	1.2 (−0.1 to 2.4)	**0.02**
T120	60	2.5 ± 2.2	64	2.1 ± 2.1	0.5 (−1.0 to 2.1)	0.20
Number of doses given						
One dose		58 (50.0)		42 (35.3)		0.07
Two doses		25 (21.4)		29 (24.4)		
Three doses		34 (29.1)		48 (40.3)		

The bold numbers indicate the significant values that were recorded.

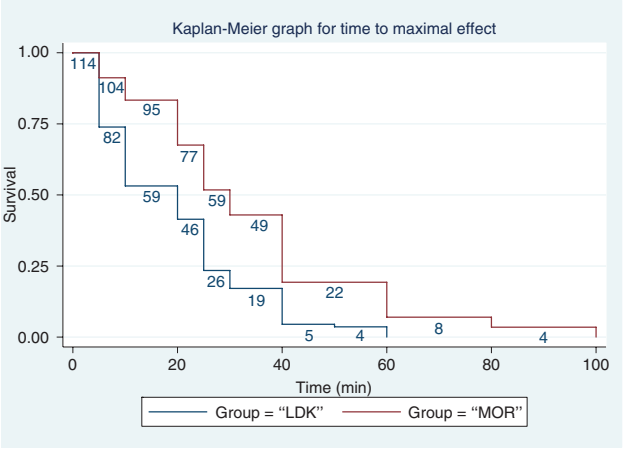

Fig. 2: Kaplan-Meier survival estimates for time to maximal change in NRS pain score from baseline.

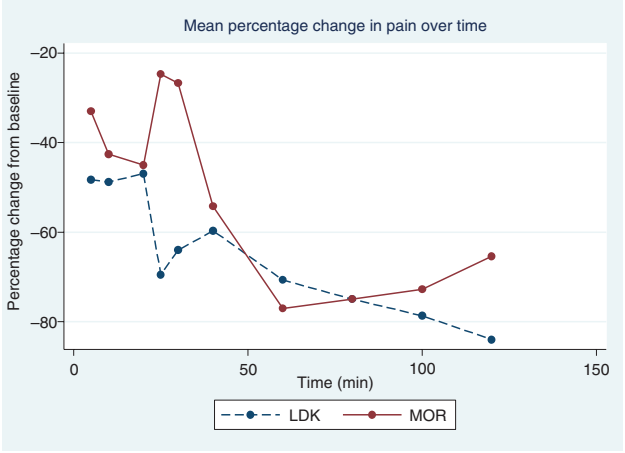

Fig. 3: Mean Numeric Rating Score as a percent change from baseline over time.

required more doses therefore had more numbers available for analysis at those times creating a random error that exaggerated percentage reduction in LDK arm.

LDK had a significantly shorter time to maximal effect compared to MOR and this was consistent with literature elsewhere [24, 38, 39]. However the ketamine onset was

Table 3: Frequency of side effects among patients receiving ketamine or morphine in managing severe painful sickle cell crises in children at Mulago hospital.

Time	Frequency of side effects *n* (%)[a]						
	Nystagmus	Dysphoria	Dizziness	Allergy	Nausea vomiting	Saliva	Pruritus
5 min							
LDK	18 (15)	12 (10)	4 (3.3)	0 (0)	2 (1.7)	2 (1.7)	0 (0)
MOR	0 (0)	0 (0)	1 (0.8)	2 (1.7)	0 (0)	0 (0.0)	2 (1.7)
10 min							
LDK	5 (4.2)	8 (6.7)	4 (3.3)	0 (0)	0 (0)	0 (0)	0 (0)
MOR	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)
25 min							
LDK	0 (0)	2 (1.7)	0 (0)	0 (0)	1 (1.7)	4 (3.3)	0 (0)
MOR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a]Denominator for the percentages are the total patients in each arm (120).

Table 4: Frequency of interventions among patients receiving low-dose ketamine or morphine in managing severe painful sickle cell crises in children at Mulago hospital.

Time	Group	Intervention *n* (%)[a]			
		Midazolam	Atropine	Ondansetron	Hydrocortisone
5 min	LDK	0 (0.0)	2 (1.7)	2 (1.7)	0 (0)
	MOR	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.3)
10 min	LDK	8(6.7)	0 (0.0)	0 (0.0)	0 (0)
	MOR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)
25 min	LDK	0 (0)	4 (3.3)	1 (0.8)	0 (0)
	MOR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)

No oxygen or naloxone was used.
[a]Denominator for the percentages are the total patients in each arm (120).

significantly longer compared to prior studies [38, 39]. A plausible explanation to this is that we were unable to assess pain before 20 min in some patients due to either disorientation or light sedation.

The maximum reduction of NRS pain scores with LDK was sustained for an hour with an additional 37.5% of the patients maintaining this degree of pain relief throughout the 2 h study period. This is contrary to prior studies [38, 39] however, relates to the higher dose and longer infusion time used.

An 11-fold increase of side effects in the ketamine arm was noted and were 7.5 times more likely to occur at T5 and disappear by T25. Nystagmus, dysphoria and salivation were the commonest adverse effects for ketamine. Morphine arm recorded mild allergic reactions although one patient was terminated with urticaria as a precautionary measure because he required a second dose. All were transient, non-life threatening and anticipated effects.

The adverse effect rate is documented at 6–58% for LDK and 14–57% for MOR from other studies [23, 31, 34, 36–39]. Our findings are within the ketamine range. We hypothesize that ketamine had less side effects due to the longer infusion time (10 min) however, the higher dose infused (1 mg/kg) could explain the observed difference. Longer infusion times or reduction of dose (per kg) will be required to further reduce side effect profile while maximizing analgesic potential.

The longer time to onset of action and probable opioid tolerance contributed to increased rate of repeat dosing in morphine (40.3%) vs. ketamine (29.8%) as more patients had suboptimal pain control. Whereas the higher dose coupled with longer infusion time reduced ketamine failures seen in previous studies [23, 34].

There were several limitations with our study. Firstly it was a single centre trial which could limit generalizability. However, it is the only Sickle cell day care center in Uganda. It has over 7,000 patients registered with it and on average sees 200 patients 5 days a week. Secondly, pain assessment was done at particular intervals that limited our ability to determine the exact time of onset and consequently duration of action of the drugs, we however

covered for this in our stratified analysis. NRS is not a validated tool for pain assessment in pediatrics, we enrolled an older population (7–18 years) who were able to comprehend the scale and this was explained at every assessment point and had to be validated thrice before it was recorded. The Ramsay Sedation Scale used in our study is not validated tool for assessment of sedation in the pediatrics however it summarized a range of effects that helped the study team quickly assess for sedation effects in this population, as it was easy to use and reproducible. Lastly, some patients exhibited known ketamine specific effects like nystagmus which created a potential for possible un-blinding.

Despite these limitations, this study demonstrates efficacy of ketamine and we can conclude that ketamine at 1 mg/kg as an infusion over 10 min is as effective as morphine 0.1 mg/kg in management of acute VOC in the pediatric population. At 1 mg/kg ketamine is associated with transient, non-life threatening side effects suggesting it safe for use in acute severe VOC with careful monitoring. Further studies on optimal infusion rate for ketamine to minimize side effects are required.

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Authors' statements

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Informed consent: Parental consent and child assent for children above 8 years was obtained from all participants.

Ethical approval: This study was approved by the Makerere University, School of Medicine Research and Ethics Committee (SOMREC) and was registered to the clinical trials.gov registry with identifier number NCT02434939.

Author contributions

Dr. Lubega hand in hand with his supervisors developed this idea from conceptualization to final proposal. Dr. MSD primarily assisted in data collection and training research assistants. Drs. LTS and MD supervised proposal development, oversaw study design, data analysis plus results review through to dissertation completion. Drs. JT, PKA, RN, FB & LTN were involved in final manuscript writing.

References

[1] Benjamin LJ, Dampier CD, Jacox A, Odesina V, Phoenix D, Shapiro B, Strafford M, Treadwell M. Guideline for the management of acute and chronic pain in sickle cell disease. APS Clinical Practice Guidelines Series, No. 1. Glenview, Il.: American Pain Society, 1999:12–3.

[2] Dampier C. The management of pain from sickle cell disease. In: Benzon H, Rathmell J, Wu C, Turk DC, Argoff C, Hurley R, editors. Practical Management of Pain. Philadelphia, PA: Mosby, 2014:997–1002.

[3] Frenette PS. Sickle cell vaso-occlusion: multistep and multicellular paradigm. Curr Opin Hematol 2002;9:101–6.

[4] Elander J, Lusher J, Bevan D, Telfer P, Burton B. Understanding the causes of problematic pain management in sickle cell disease: evidence that pseudoaddiction plays a more important role than genuine analgesia dependence. J Pain Symptom Manage 2004;27:156–9.

[5] Zempsky WT, Loiselle KA, McKay K, Blake GL, Hagstrom JN, Schechter NL, Kain ZN. Retrospective evaluation of pain assessment and treatment for vasoocclusive episodes in children with sickle cell disease. Pediatr Blood Cancer 2008;51:265–8.

[6] Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: a critical reappraisal. Blood 2012;120:3647–56.

[7] Jacob E, Mueller BU. Pain experience of children with sickle cell disease who had prolonged hospitalizations for acute painful episodes. Pain Med 2008;9:13–21.

[8] Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease – life expectancy and risk factors for early death. N Engl J Med 1994;330:1639–44.

[9] Panepinto JA, Brousseau DC, Hillery CA, Scott JP. Variation in hospitalizations and hospital length of stay in children with vaso-occlusive crises in sickle cell disease. Pediatr Blood Cancer 2005;44:182–6.

[10] Yang YM, Shah AK, Watson M, Mankad VN. Comparison of costs to the health sector of comprehensive and episodic health care for sickle cell disease patients. Pub Health Rep 1995;110:80–6.

[11] Dunlop RJ, Bennett KC. Pain management for sickle cell disease. Cochrane Database Syst Rev 2006:CD003350.

[12] Yoon SL, Black S. Comprehensive, integrative management of pain for patients with sickle cell disease. J Altern Complement Med 2006;12:995–1001.

[13] Campbell CM, Moscou-Jackson G, Carroll CP, Kiley K, Haywood C, Lanzkron S, Hand M, Edwards RR, Haythornthwaite JA. An evaluation of central sensitization in patients with sickle cell disease. J Pain 2016;17:617–27.

[14] Mitra S. Opioid-induced hyperalgesia: pathophysiology and clinical implications. J Opioid Manag 2007;4:123–30.

[15] Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011;14:145–61.

[16] Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. Clin J Pain 2008;24:479–96.
[17] DuPen A, Shen D, Ersek M. Mechanisms of opioid-induced tolerance and hyperalgesia. Pain Manag Nurs 2007;8:113–21.
[18] Darbari DS, Neely M, VandenAnker J, Rana SR. Morphine pharmacokinetics in sickle cell disease: implications for pain management. Blood 2009;114:2574.
[19] Dampier CD, Setty B, Logan J, Ioli JG, Dean R. Intravenous morphine pharmacokinetics in pediatric patients with sickle cell disease. J Pediatr 1995;126:461–7.
[20] Joubert K. Ketamine hydrochloride-an adjunct for analgesia in dogs with burn wounds. J S Afr Vet Ass 1998;69:95–7.
[21] Fisher K, Coderre TJ, Hagen NA. Targeting the NMDA receptor for chronic pain management: preclinical animal studies, recent clinical experience and future research directions. J Pain Symptom Manage 2000;20:358–73.
[22] Neri CM, Pestieau SR, Darbari DS. Low-dose ketamine as a potential adjuvant therapy for painful vaso-occlusive crises in sickle cell disease. Pediatr Anesth 2013;23:684–9.
[23] Zempsky WT, Loiselle KA, Corsi JM, Hagstrom JN. Use of low-dose ketamine infusion for pediatric patients with sickle cell disease-related pain: a case series. Clin J Pain 2010;26:163–7.
[24] Jennings CA, Bobb BT, Noreika DM, Coyne PJ. Oral ketamine for sickle cell crisis pain refractory to opioids. J Pain Palliat Care Pharmacother 2013;27:150–4.
[25] Uprety D, Baber A, Foy M. Ketamine infusion for sickle cell pain crisis refractory to opioids: a case report and review of literature. Ann Hematol 2014;93:769–71.
[26] Finkel JC, Pestieau SR, Quexado ZMN. Ketamine as an adjuvant for the treatment of cancer pain in children and adolescents. J Pain 2007;8:515–21.
[27] Fine PG. Low-dose ketamine in the management of opiod nonresponsive terminal cancer pain. J Pain Symptom Manage 1999;17:296–300.
[28] Tsui BC, Davies D, Desai S, Malherbe S. Intravenous ketamine infusion as an adjuvant to morphine in a 2-year-old with severe cancer pain from metastatic neuroblastoma. J Pediatr Hematol Oncol 2004;26:678–80.
[29] Bartoc C, Frumento RJ, Jalbout M, Bennet-Guerrero E, Du E, Nishanian E. A randomised, double-blind, placebo-controlled study assessing the anti-inflammatory effects of ketamine in cardiac surgical patients. J Cardiothorac Vasc Anesth 2006;20:217–22.
[30] Luggya TS, Roche T, Ssemogerere L, Kintu A, Kasumba JM, Kwizera A, Tindimwebwa JV. Effect of low-dose ketamine on post-operative serum IL-6 production among elective surgical patients: a randomized clinical trial. Afr Health Sci 2017;17:500–7.
[31] Green SM, Krauss B. Ketamine is safe, effective and appropriate technique for emergency department pediatric procedural sedation. Emerg Med J 2004;21:271–3.
[32] Green SM, Rothrock SG, Lynch EL, Ho M, Harris T, Hestdalen R, Hopkins GA, Garrett W, Westcott K. Intravenous ketamine for pediatric sedation in the emergency department: safety profile in 1022 cases. Ann Emerg Med 1998;31:688–97.
[33] Meals CG, Mullican BD, Shaffer CM, Dangerfield PF, Ramirez RP. Ketamine infusion for sickle cell crisis pain in an adult. J Pain Symptom Manage 2011;42:7–9.
[34] Neri CM, Pestieau SR, Young H, Elmi A, Finkel JC, Darbari DS. Low-dose ketamine for children and adolescents with acute sickle cell disease related pain: a single center experience. J Anesth Clin Res 2014;5:394.
[35] Tawfic QA, Faris AS, Kausalya R. The role of a low-dose ketamine-midazolam regimen in the management of severe painful crisis in patients with sickle cell disease. J Pain Symptom Manage 2014;47:334–40.
[36] Ahern TL, Herring AA, Anderson ES, Madia VA, Fahimi J, Frazee BW. The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. Am J Emerg Med 2015;33:197–201.
[37] Neri CM, Pestieau S, Young H, Elmi A, Darbari DS. Safety and efficacy of adjuvant low-dose ketamine therapy for patients with sickle cell disease. Blood 2012;120:3226.
[38] Motov S, Rockoff B, Cohen V, Pushkar I, Likourezos A, McKay C, Soleyman-Zomalan E, Homel P, Terentiev V, Fromm C. Intravenous subdissociative-dose ketamine versus morphine for analgesia in the emergency department: a randomized controlled trial. Ann Emerg Med 2015;66:222–9.e221.
[39] Miller JP, Schauer SG, Ganem VJ, Bebarta VS. Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial. Am J Emerg Med 2015;33:402–8.