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ORIGINAL CONTRIBUTION

Ketamine administration for acute painful sickle cell crisis: A randomized controlled trial

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Abstract

Objective: The objective was to evaluate the efficacy and safety of single-dose ketamine infusion in adults with sickle cell disease (SCD) who presented with acute sickle vasoocclusive crisis (VOC).

Methods: This study was a parallel-group, prospective, randomized, double-blind, pragmatic trial. Participants were randomized to receive a single dose of either ketamine or morphine, infused over 30 min. Primary outcome was mean difference in the numerical pain rating scale (NPRS) score over 2 h. NPRS was recorded every 30 min for a maximum of 180 min and secondary outcomes were cumulative dose of opioids, emergency department (ED) length of stay, hospital admission, change in vital signs, and drug-related side effects. Authors performed the analysis using intention-to-treat principle.

Result: A total of 278 adults with SCD and who presented with acute sickle VOC participated in this trial. A total of 138 were allocated to the ketamine group. Mean (±standard deviation [SD]) NPRS scores over 2 h were 5.7 (±2.13) and 5.6 (±1.90) in

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the ketamine and morphine groups. The ketamine group received significantly lower cumulative doses of morphine during their ED stay (mean ± SD = 4.5 ± 4.6 mg) than of the morphine group (mean ± SD = 8.5 ± 7.55 mg). Both groups had similar rates of hospital admission: 6.3% in the ketamine group had drug-related side effects compared to 2.2% in the morphine group.

Conclusion: Early use of ketamine in adults with VOC resulted in a meaningful reduction in pain scores over a 2-h period and reduced the cumulative morphine dose in the ED with no significant drug-related side effects in the ketamine-treated group.

INTRODUCTION

Sickle cell disease (SCD) is a hereditary hematologic disorder in which deoxygenated hemoglobin polymerizes, resulting in the sickle-like shape of red blood cells. These rigid, misshapen cells trigger vasoocclusion in the microcirculation, resulting in tissue ischemia. In addition, damage to the red blood cell membrane causes chronic hemolytic anemia.[1–4]

Vasoocclusive crisis (VOC) is the most common complication of SCD and is associated with severe pain that may recur frequently, requiring emergency department (ED) visits and hospitalization. Patients who are frequently hospitalized because of painful VOC are at a higher risk of early death.[5–8]

The cost of hospital admission for SCD patients is on the rise. In 2017, the public heath registry recorded approximately 14,000 individuals living with SCD in the UK; indicating that one in 4600 people living in the UK have SCD.[9] In the US, a study conducted in 2009 revealed that SCD affected close to 100,000 individuals and cost more than $1.1 billion.[10]

Although SCD is prevalent in Saudi Arabia, studies show significant variations in its prevalence across the country. The occurrence in the Eastern province is 145 cases/10,000 residents, 24 cases/10,000 in the Southern Province, 12 cases/10,000 in the Northern Province, 6 cases/10,000 in the Western and Central Provinces, respectively.[11–14]

Standard therapy for VOC includes intravenous (IV) hydration and opioid analgesia. Although existing evidence supports the use of opioid therapy for the treatment of VOC,[15–19] treating physicians often encounter challenges when attempting to balance the analgesic and adverse effects of opioids. A cross-sectional survey of 721 ED physicians found that emergency physicians who attend to more than one SCD patient per week were inclined to have negative attitude toward SCD patients and were less likely to redose opioids within 30 min for inadequate analgesia.[20] Commonly reported side effects of opioids are drowsiness, nausea, abdominal pain, confusion, and respiratory depression with variable incidence.[21–24] Similar to other patients receiving treatment for chronic or recurrent pain, SCD patients may experience opioid-induced hyperalgesia, an enhanced pain response owing to the activation of the *N*-methyl-D-aspartate (NMDA) receptors.[25]

Ketamine, a noncompetitive NMDA receptor antagonist, may modulate opioid-induced hyperalgesia by impairing the sensitization of the spinal neurons to nociceptive stimuli.[26] Ketamine acts on glutamate and NMDA receptors, which modulate the peripheral pain sensitization process along the pain pathways. Ketamine is also proposed to affect neural plasticity on the NMDA and the spinal pathway by preventing the transmission of the generated stimuli toward the central nervous system.[27,28] Thus, ketamine may reduce pain. Because patients with long-term exposure to opioid therapy are prone to drug-related dependency, the administration of ketamine therapy may minimize this.[29–32] To date, only one randomized clinical trial (RCT) that enrolled children with VOC who were randomly administered ketamine or morphine has been published which found that ketamine was noninferior to morphine at reducing pain scores, with authors reporting increased adverse events in the ketamine arm, although they were mild and transient.[33] Presently, the effect of adding ketamine to the treatment regimen for adults with VOC is unclear. Furthermore, there are no published RCTs investigating the effect of low-dose ketamine on pain scores in adults with VOC. Thus, we opted to perform a large RCT to evaluate this therapy.

METHODS

Trial design

This study was a parallel-group, prospective, randomized, blinded, pragmatic, controlled trial that sought to evaluate the efficacy and safety of single-dose ketamine infusion in addition to the usual care relative to those of morphine, for the management of sickle VOC. Ethical approval was granted by the institutional review board at Imam Abdulrahman Bin Faisal University. Between January 2018 and February 2019, patients were recruited at the

ED of King Fahd Hospital, the largest tertiary academic international accredited hospital in the Eastern Province of Saudi Arabia; this hospital has an average number of ~180,000 ED patient visits per year.

We registered the trial protocol online (Clinicaltrials.gov registration NCT03431285) and, subsequently, published the full protocol.[34] All authors affirm the accuracy and completeness of the data and adherence to the approved protocol.

Participants

We enrolled adults 18 years and older with SCD, confirmed hemoglobin electrophoresis results consistent with any SCD genotype (homozygous hemoglobin S [HbSS], compound heterozygous S with C [HbSC], or sickle beta thalassemia [HbSβ] or any other genotypes), and numeric pain rating scale (NPRS) score > 5, who presented with acute sickle VOC with onset within the 7 days prior to ED visit. Exclusion criteria were pregnant or breast-feeding women, patients with body mass index of >40 kg/m^2, known neurological disease, seizures, acute head or eye injury, psychiatric disorders, known cardiac diseases, known pulmonary diseases besides acute chest syndrome, renal disease, chronic liver disease, allergic to the study drugs, sepsis or septic shock, need for circulatory or ventilatory support, alcohol or drug abuse, or known chronic pain that is unrelated to SCD.

Randomization, blinding, and treatment

Patients were randomized using a block size of six into online, computer-generated program, which concealed randomization and treatment allocation. Patients were assigned to a 1:1 ratio to receive and either a single low-dose of ketamine (0.3 mg/kg) in 100 ml of normal saline or a standard dose of morphine (0.1 mg/kg) in 100 ml of normal saline. All patients received standardized IV hydration. Participants, health care providers, data collectors, and outcome assessors were blinded to the treatment allocation. To ensure blinding, we used 100-ml normal saline bags with similar appearance and consistency.

Study procedures

Upon eligibility confirmation and written consent, demographics, NPRS, Richmond Agitation Sedation Scale (RASS), and clinical variables (pulse rate, respiratory rate, blood pressure, and oxygen saturation) were collected by trained study nurses. Normal saline or Ringer's lactate was administered at a maintenance rate through a peripheral IV line, as per pre-designed pathway (Appendix S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14382/full). In addition, prior to administering the study intervention, ED physicians were allowed to prescribe a nonnarcotic preanalgesia of either IV paracetamol 1-g infusion or nonsteroidal anti-inflammatory drugs, either lornoxicam 8–16 mg IV or diclofenac 75-mg intramuscular injection. The choice of analgesic was based on the treating physician's discretion. At 30 min following the initial administration of the nonopioid analgesia, patients with NPRS score above 5 were enrolled in the study.

An independent study nurse randomized patients via an online, computer-generated random sequence wherein the treatment allocation was concealed. An infusion bag was then prepared and labeled by the same independent study nurse according to the sequential randomization code, covered in an opaque foil bag, and handed to the blinded bedside nurse who administered the study drug via infusion to the study participant over 30 min. The bedside blinded nurse documented vital signs, RASS, and NPRS of patients every 30 min for a minimum of 30 min and a maximum of 180 min. The ED treating physician discharged patients after a minimum of 120 min of receiving study drug if all the following criteria were fulfilled: patient is fully awake, vital signs were normal, able to walk independently, and absence of any study drug side effect. Conversely, the admission decision was taken within a maximum of 180 min if the following situations occurred: patients' NPRS score remained more than 5, unstable vital signs for any reason, any side effects assumed to be related to study drug, or at the ED physician's discretion. Drug-related adverse events were recorded and monitored and were treated accordingly.

End points

The primary outcome was pain rated by NPRS. Patients blinded to the study drug were asked to rate their pain at the initial assessment, and the score was recorded by the bedside nurse every 30 min for a minimum of 30 min and a maximum of 180 min. Pain was measured on a scale from 0 (no pain) to 10 (the worst pain).

Secondary outcomes were the cumulative dose of opioids administered including the intervention dose, the length of ED stay (defined as the time from the start of administration of the study medication to discharge home or admission), hospital admission rate, difference in RASS scores, patient's hemodynamic parameters, heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SpO_2), and drug-related adverse effects.

Blinded attending physicians in the ED performed patient management and administered rescue pain medications at their discretion. Patients were discharged after a minimum of 120 min if they met the predefined criteria described earlier. Patients with an NPRS score > 5 were admitted to the hospital within a maximum 180 min.

For the administration of the study drugs, the treating team adhered to the standard practice policies and procedures for administering high-alert medications according to The Joint Commission international standards.[35] Patients were also monitored by the bedside nurse to identify any ketamine or morphine-related adverse effects.

Data analysis

A priori pilot study that included 10 patients with SCD who received morphine or ketamine for VOC was performed. The standard deviation (SD) of 3.4 was derived from this pilot study and with assumption of a mean difference of NPRS of 1.5 between both groups, a power of 90%, and a type 1 error rate of 5%, our sample size calculation suggested at least 120 participants per group were required. This sample size estimation is based on a two-sided test of the null hypothesis that there is no difference between groups. To compensate for patients who might withdraw from the study, we planned to enroll additional patients (10%) to achieve a final sample size of 264 patients. These computations were done using PS: Power and Sample Size Calculations version 3.1.6, which was developed by William D. Dupont and Walton D. Plummer Jr.[36] An independent statistician and data monitoring team carried out three interim analyses: at 25% (70 patients), 50% (140 patients), and 75% (210 patients). Data evaluation at each interim analysis was based on the alpha spending function concept using the Lan-DeMets O'Brien Fleming approach and the two-sided, asymmetric, beta-spending with nonbinding lower bound.[37,38]

The intention-to-treat principle was used for all analyses and multiple imputation techniques (Markov chain Monte Carlo algorithm–fully conditional specification was used to replace missing data). Categorical variables are presented as absolute numbers and percentages while continuous variables are expressed as mean (±SD) or median and interquartile range. Normality was evaluated by visual histogram evaluation and a Q-Q plot. Between-group differences were evaluated using t-test or a chi-square test, as appropriate. For repeated-measures continuous outcomes (NPRS, RASS, HR, MAP, SpO_2), we used generalized estimation equations to model the average differences between groups over time. For these models, we used a linear (normally distributed data) or gamma (skewed data) link and an autoregressive integrated moving average (ARIMA) 1 correlation matrix. We entered the allocation group (ketamine or morphine) as the predictor. The level of significance was set at $\alpha = 0.05$. For all analyses, mean difference (MD) or odds ratios (OR), corresponding 95% confidence intervals (CIs), and *p*-values are reported. All analyses were conducted using SPSS version 25 (IBM).

RESULTS

Patients

Between January 2018 and February 2019, a total of 314 patients were assessed for their eligibility to participate in this study. Thereafter, 306 patients were deemed eligible for study participation but 28 declined to participate. A total of 278 patients were thus enrolled and randomized. A total of 138 patients were assigned to the ketamine group and 140 patients to the morphine group.

Baseline characteristics were similar between the groups (Table 1). Mean (±SD) age was 29.4 (±8.1) years, mean (±SD) NPRS at randomization was 8.6 (±1.3), and mean (±SD) NPRS scores for the ketamine group and morphine group were 8.6 (±1.3) and 8.7 (±1.3), respectively. Eighty-three patients were taking hydroxyurea, 42 and 41 of whom were in the ketamine and morphine groups, respectively. The most common genotype was HbSC (156 [56.1%] cases), followed by HbS/β-thalassemia (84 [30.2%] cases). Median RASS ranged from 0 to 4 (min–max), with a slightly lower maximum scale in the ketamine group (0–2) than the morphine group (0–4).

Primary end point

Throughout the study period, NPRS did not differ significantly between groups in the intention-to-treat analysis (MD = 0.13 points, 95% CI = −0.34 to 0.60, $p = 0.63$), which align with the findings of the sensitivity per-protocol analysis (Table 2, Figure 1A).

Secondary end points

According to the intention-to-treat analysis, ketamine use reduced the mean cumulative dose of opioids compared to morphine group, 0.07 mg/kg versus 0.13 mg/kg (MD = 0.061, 95% CI = 0.038 to 0.083, $p < 0.001$). No significant difference was found in hospital admission between the two groups; 26 patients (20.3%) in the ketamine group and 34 patients (24.6%) in the morphine group were admitted to the hospital (OR = 0.71, 95% CI = 0.44 to 1.39, $p = 0.4$).

A total of 12 adverse events occurred in 11 patients (nine of whom were treated with ketamine; OR = 2.81, 95% CI = 0.65 to 16.74, $p = 0.13$). Five patients in the ketamine group developed dizziness versus three in the morphine group, while four patients in the ketamine group developed nausea and vomiting. Other outcomes, including changes in RASS, MAP, and SPO_2, were similar between the groups (Table 2, Figure 1A,B).

DISCUSSION

In this RCT of 278 adult patients with acute sickle VOC, we found that the ketamine-based regimen was not superior to the morphine-based regimen in reducing pain score. However, ketamine treatment was associated with significantly reduced cumulative dose of opioids. Other outcomes, including adverse events and hemodynamic parameters, did not differ between the two groups.

Tolerance to opioids and opioid-induced hyperalgesia could contribute to the refractory nature of pain in sickle VOC to opioids.[39] Herein, we found clinically meaningful improvement in pain, demonstrated by an improvement in the NPRS score in both groups; however, the ketamine-based regimen was not superior to morphine alone, as we hypothesized. To the best of our knowledge, this is the largest and the only RCT to investigate the efficacy of ketamine relative to morphine in adults. An extensive search of the literature revealed few studies on the use of low-dose ketamine in

TABLE 1 Distribution of baseline characteristics by group

Variable	Ketamine ($n = 138$)	Morphine ($n = 140$)	Total ($N = 278$)
Age (years)	29.1 (±8.4)	29.6 (±7.9)	29.4 (±8.1)
Gender (female)	58 (42.0)	58 (41.4)	116 (41.7)
Weight (kg)	65.8 (±17.85)	67.2 (±15.54)	66.4 (±16.7)
Allergies	3 (2.2)	3 (2.1)	6 (2.2)
Smoking status (yes)	3 (2.2)	5 (3.6)	8 (2.9)
Currently receiving hydroxyurea (yes)	42 (30.4)	41 (29.3)	83 (29.9)
Genotype			
SS	10 (7.2)	23 (16.4)	33 (11.9)
SB	42 (30.4)	42 (30.0)	84 (30.2)
SC	83 (60.1)	73 (52.1)	156 (56.1)
SD	2 (1.4)	2 (1.4)	4 (1.4)
SE	1 (0.7)	0 (0.0)	1 (0.4)
Count (% within group)	138 (100.0)	140 (100.0)	278 (100.0)
Comorbidities (yes)	7 (5.0)	7 (5.0)	14 (5.0)
Comorbidities[a]			
ACS or pneumonia	0 (0.0)	1 (0.7)	1 (0.4)
AVN	1 (0.7)	2 (1.4)	3 (1.1)
Systemic hypertension	1 (0.7)	1 (0.7)	2 (0.7)
Myocardial infarction	0 (0.0)	1 (0.7)	1 (0.4)
Arrhythmia	1 (0.7)	0 (0.0)	1 (0.4)
Other pulmonary disease	1 (0.7)	1 (0.7)	2 (0.7)
Hepatic disease	1 (0.7)	0 (0.0)	1 (0.4)
DM	0 (0.0)	1 (0.7)	1 (0.4)
Others	3 (2.2)	1 (0.7)	4 (1.4)
Type of preanalgesia			
Paracetamol	61 (44.5)	57 (41.0)	118 (42.8)
NSAIDs	76 (55.5)	82 (59.0)	158 (57.2)
NPRS[b]	8.6 (±1.3)	8.7 (±1.3)	8.6 (±1.3)
RASS, median (range)[b]	0 (0–2)	0 (0–4)	0 (0–4)
HR[b]	88.2 (±14.4)	82.0 (±15.43)	85.1 (±15.6)
RR[b]	20.1 (±1.4)	20.2 (±1.6)	20.2 (±1.5)
SBP[b]	123.4 (±16.4)	124.2 (±16.5)	123.8 (±16.4)
DBP[b]	75.2 (±12.4)	77.4 (±15.1)	76.3 (±13.8)
MAP[b]	91.3 (±12.3)	92.9 (±14.5)	92.1 (±13.5)
T[b]	36.6 (±2.9)	36.7 (±0.63)	36.6 (±2.1)
SpO_2[b]	97.7 (±1.7)	97.3 (±2.4)	97.5 (±2.1)

Note: Data are reported as mean (±SD) or *n* (%), unless otherwise specified.

Abbreviations: DBP, diastolic blood pressure; DM, diabetes mellitus; HR, heart rate; MAP, mean arterial pressure; NPRS, numerical pain rating scale; NSAID, nonsteroidal anti-inflammatory drug; RASS, Richmond Agitation Sedation Scale; SBP, systolic blood pressure; SpO_2, blood oxygen saturation.

[a]Not mutually exclusive (two people presented two comorbidities).

[b]One missing from each group.

the management of VOC. The results from most published research of ketamine in this population are limited by observational design and small sample sizes. Three earlier studies compared ketamine to morphine in this context: two included children while the third had a small sample size. Altogether, these studies had inconsistent results. One RCT comparing ketamine to morphine for the treatment of 240 children with acute VOC revealed that ketamine was noninferior to morphine at reducing pain scores. Authors used a higher ketamine

TABLE 2 Outcome analysis

Outcomes	Ketamine ($n = 138$)	Morphine ($n = 140$)	Effect (95% CI)	p-value
Primary				
NPRS				
Intention to treat	5.7 (±2.13)	5.6 (±1.90)	MD 0.13 (−0.34–0.60)	0.625
Per protocol	6.9 (±5.27)	6.8 (±4.11)	MD 0.16 (−0.96–1.27)	0.780
Secondary				
Accumulative morphine dose (mg/kg)	0.07 (±0.07)	0.13 (±0.11)	MD 0.061 (0.038–0.083)	<0.001
Number of rescue morphine orders after intervention (mg/kg)	0.89 (±0.88)	0.9 (±1.44)	MD 0.008 (−0.272–0.290)	0.802
Tramadol used (yes)	6 (4.3)	10 (7.1)	OR 0.59 (0.20–1.67)	0.441
Hospital admission[a]	26 (20.3)	34 (24.6)	OR 0.71 (0.44–1.39)	0.399
Any adverse events (yes)[a,b]	8 (6.3)	3 (2.2)	OR 2.81 (0.65–16.74)	0.136
Dizziness	5 (3.9)	3 (2.2)		
Nausea	4 (3.1)	0 (0.0)		
Vomiting	1 (0.8)	0 (0.0)		
RASS	1.09 (±0.60)	1.18 (±0.85)	MD −0.09 (0.08)	0.324
MAP	88.8 (±9.89)	90.3 (±10.90)	MD −1.41 (1.25)	0.261
SpO_2	97.8 (±1.29)	97.7 (±1.51)	MD 0.15 (0.17)	0.382
Time to discharge				
Minutes	281.3 (±119.35)	285.3 (±148.66)	MD −3.99 (−35.85–27.85)	0.805
Hours	4.7 (±1.98)	4.8 (±2.47)	MD −0.1 (−0.62–0.43)	0.710

Note: Data are reported as mean (±SD) or *n* (%), unless otherwise specified.

Abbreviations: HR, heart rate; MAP, mean arterial pressure; MD, mean difference; NPRS, numerical pain rating scale; RASS, Richmond Agitation Sedation Scale; SD, standard deviation; SpO_2, blood oxygen saturation.

[a]14 missing.

[b]Not mutually exclusive.

dose (1 mg/kg), relative to the usual analgesic dose (0.3 mg/kg), and found higher drug-related side effects in the ketamine group.[33] A retrospective observational study compared 33 children with acute sickle VOC who received low-dose ketamine and opioid patient-controlled analgesia to a control group of children who did not receive ketamine. Although this study reported higher pain scores in the ketamine group, the results might be confounded by the inclusion of patients with more severe pain in the ketamine arm.[40] Another study reported contradictory results for 30 adults with acute sickle VOC and found that low-dose ketamine infusion reduces opioid requirements.[41] Small case series of five children with sickle VOC showed that ketamine may improve pain control and reduce opiate use.[42]

In comparison to aforementioned studies, we found a low rate of side effects in the ketamine group, further supporting the safety of low-dose ketamine infusions. Compared with morphine, drug-related adverse effects, including hemodynamic changes (MAP, HR, respiratory function, and SpO_2), after a single infused dose of ketamine, were similar in both arms of our study. Other side effects, including dizziness, nausea, and vomiting, were numerically more common on our study in the ketamine-treated patients. Lubega et al.[33] found that patients in their ketamine group were 11.5 times more likely to develop nystagmus (15%) or dysphoria (11.3%), the most common side effects of ketamine treatment. These adverse events in the study by Lubega et al. are likely related to the use of high-dose ketamine (1 mg/kg). Opioids are a well-known cause of respiratory depression; however, our results did not identify any episodes of respiratory depression in either study group.

Our results are in line with other published reports that revealed that ketamine infusion had an opioid-sparing effect reducing the opioid cumulative dose required to achieve satisfactory pain control.[21,43–45] Studies in other acute clinical settings such as musculoskeletal, postoperative, and abdominal pain also suggested that ketamine may have opioid-sparing effect.[32,33]

The comparative morphine dose of 0.1 mg/kg was considered a starting dose of 0.1 mg/kg of morphine as per the authors' center protocol while allowing subsequent pragmatic administration of rescue analgesics (including morphine and tramadol) as per the discretion of the treating blinded physician, which is expectedly required for those non–opioid-naïve patients. Similarly, Lubega et al.[33] used similar dose of morphine for same group of patients.

There are several strengths of this RCT. First, this is the largest RCT in adults with VOC, which enhances the precision of the estimates of effect. The design was robust to minimize selection, performance, and attrition biases. We investigated an important

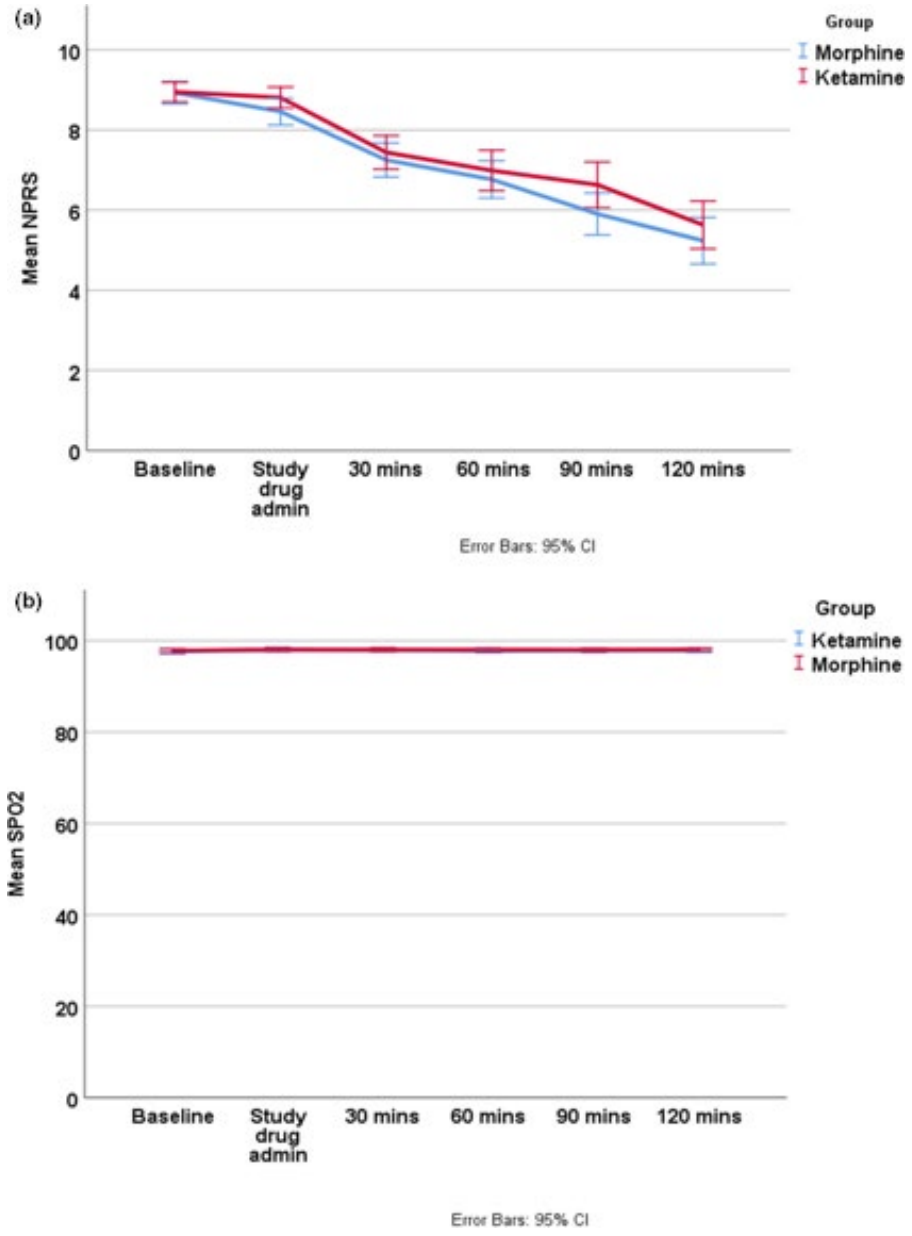

FIGURE 1 (A) Numerical Pain Rating Score (NPRS). (B) Oxygen saturation (SPO_2) [Color figure can be viewed at wileyonlinelibrary.com]

and timely clinical question, focusing on patient-important outcomes. The pragmatic design of this trial allows better generalizability of the results. Finally, we adhered to a robust analysis plan and performed sensitivity analyses using intention-to-treat and per-protocol analyses.

LIMITATIONS

Limitations included this being a single-center trial, thereby restricting the generalizability of the findings. Also, 180 min might be a short time frame to assess impact of a study drug. Despite being blinded study, some known ketamine reactions might be identified. Moreover, we calculated the use of a single low dose of ketamine that might be inadequate to provide our hypothesized superiority in the ketamine treated arm. Therefore, future studies are needed to explore the efficacy and safety of repeated ketamine dosing or continuous infusion for adults with sickle VOC and also to study the combination effect of ketamine and opioid in comparison to opioid alone.

CONCLUSION

Early use of ketamine in sickle cell disease patients with vasoocclusive crisis had a considerable analgesic effect with less accumulative morphine doses needed and with no significant safety concerns.

CONFLICT OF INTEREST

The authors have no potential conflicts to disclose.

AUTHOR CONTRIBUTIONS

Mohammed S. Alshahrani, Mohamed R. ElTahan, Laila P. Asonto, Waleed Alhazzani conceived the project. Mohammed S. Alshahrani, Amal H. AlSulaibikh, Mohamed R. ElTahan, Sukayna Z. AlFaraj, Abdullah A. AlMulhim, Murad F. AlAbbad, Shaikhah K. Alotaibi, Thamir O. AlJunaid, Nisreen Almaghraby, Alaa M. Mahmoud, Moath N. Darweesh, Faisal M. AlHawaj, Bader K. Alossaimi, Shaikhah K. Alotaibi, Reem Alhawwas, Talal M. AlMutairi, Duaa A. AlSulaiman, Dunya Alfaraj managed the trial (including recruitment and data collection) with support, input, and oversight from Mohammed S. Alshahrani. Mohamed R. ElTahan, Gordon Guyatt, Kim Lewis, Waleed Alhazzani. Mark Crowther, Madeleine Verhovsek provided content expertise and guidance on the interpretation of the results. Lawrence Mbuagbaw prepared the data and did the statistical analysis, which was interpreted by all the other authors. Mohammed S. Alshahrani, Waleed Alhazzani, and Lawrence Mbuagbaw wrote the first draft of the manuscript. All authors contributed to the design of the study and the revision of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

ETHICS APPROVAL

Ethical approval was granted by the Institutional Review Board at Imam Abdulrahman Bin Faisal University. Patients were recruited at the ED of King Fahd Hospital, the largest tertiary academic international accredited hospital in the Eastern Province of Saudi Arabia; this hospital has an average number of ~180,000 ED patient visits per year.

DATA AVAILABILITY STATEMENT

All data produced and analysed in this study are included in this article in Tables 1 and 2 and Figures 1A,B.

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REFERENCES

1. Ballas SK, Lusardi M. Hospital readmission for adult acute sickle cell painful episodes: frequency, etiology, and prognostic significance. *Am J Hematol*. 2005;79:17-25.
2. Quinn CT. Minireview: clinical severity in sickle cell disease: the challenges of definition and prognostication. *Exp Biol Med*. 2016;241:679-688.
3. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet*. 2010;376:2018-2031. https://doi.org/10.1016/S0140-6736(10)61029-X
4. Simpson S. Sickle cell disease: a new era. *Lancet Haematol*. 2019;6:e393-e394. https://doi.org/10.1016/S2352-3026(19)30111-5
5. Van Tuijn CF, van Beers EJ, Schnog JJ, Biemond BJ. Pain rate and social circumstances rather than cumulative organ damage determine the quality of life in adults with sickle cell disease. *Am J Hematol*. 2010;85:532-535.
6. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994;330:1639-1644.
7. Houston-Yu P, Rana SR, Beyer B, Castro O. Frequent and prolonged hospitalizations: a risk factor for early mortality in sickle cell disease patients. *Am J Hematol*. 2003;72:201-203.
8. Evidence based management of sickle cell disease. U.S Department of Health and Human Services. 2014. https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Accessed January 30, 2021.
9. Dormandy E, James J, Inusa B, Rees D. How many people have sickle cell disease in the UK? *J Public Health*. 2018;40:e291-e295. https://doi.org/10.1093/pubmed/fdx172
10. Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG. The cost of health care for children and adults with sickle cell disease. *Am J Hematol*. 2009;84:323-327.
11. Lehmann H, Maranjian G, Mourant AE. Distribution of sickle-cell hemoglobin in Saudi Arabia. *Nature*. 1963;198:492-493.
12. Al-Qurashi MM, El-Mouzan MI, Al-Herbish AS, Al-Salloum AA, Al-Omar AA. The prevalence of sickle cell disease in Saudi children and adolescents. A community-based survey. *Saudi Med J*. 2008;29:1480-1483.
13. Jastaniah W. Epidemiology of sickle cell disease in Saudi Arabia. *Ann Saudi Med*. 2011;31:289-293. https://doi.org/10.4103/0256-4947.81540
14. El-Hazmi MA, Warsy AS. Appraisal of sickle-cell and thalassaemia genes in Saudi Arabia. *East Mediterr Health J* 1999;5:1147-1153.
15. Jacobson SJ, Kopecky EA, Joshi P, Babul N. Randomised trial of oral morphine for painful episodes of sickle-cell disease in children. *Lancet*. 1997;350:1358-1361.
16. Wright SW, Norris RL, Mitchell TR. Ketorolac for sickle cell vaso-occlusive crisis pain in the emergency department: lack of a narcotic-sparing effect. *Ann Emerg Med*. 1992;21:925-928.
17. Brookoff D, Polomano R. Treating sickle cell pain like cancer pain. *Ann Intern Med*. 1992;116:364-368.
18. Solomon LR. Pain management in adults with sickle cell disease in a medical center emergency department. *J Natl Med Assoc*. 2010;102:1025-1032.
19. Palm N, Floroff C, Hassig TB, Boylan A, Kanter J. Low-dose ketamine infusion for adjunct management during vaso-occlusive episodes in adults with sickle cell disease: a case series. *J Pain Palliat Care Pharmacother*. 2018;32:20-26.
20. Glassberg JA, Tanabe PN, Chow A, et al. Emergency provider analgesic practices and attitudes towards patients with sickle cell disease. *Ann Emerg Med*. 2013;62(4):293-302.e10. https://doi.org/10.1016/j.annemergmed.2013.02.004
21. Papaleontiou M, Henderson CR Jr, Turner BJ, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2010;58(7):1353-1369.
22. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112(3):372-380.
23. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ*. 2006;174(11):1589-1594.
24. Brown RT, Zuelsdorff M, Fleming M. Adverse effects and cognitive function among primary care patients taking opioids for chronic nonmalignant pain. *J Opioid Manag*. 2006;2(3):137-146.

25. Hassell K, Ngongo W, Montgomery R, Hornick L. (374) Ketamine infusion as an analgesic adjunct in the management of severe pain in patients with sickle cell disease. *J Pain*. 2017;18:S68. https://doi.org/10.1016/j.jpain.2017.02.348
26. Uzun B, Kekec Z, Gurkan E. Efficacy of tramadol versus meperidine in vaso-occlusive sickle cell crisis. *Am J Emerg Med*. 2010;28:445-449.
27. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand*. 1997;41:1124-1132.
28. Fathollahi Y, Salami M. The role of *N*-methyl-D-aspartate receptors in synaptic plasticity of rat visual cortex in vitro: effect of sensory experience. *Neurosci Lett*. 2001;306:149-152.
29. Wang ZJ, Wilkie DJ, Molokie R. Neurobiological mechanisms of pain in sickle cell disease. *Hematol Am Soc Hematol Educ Program*. 2010;2010:403-408.
30. Gonzalez ER, Ornato JP, Ware D, Bull D, Evens RP. Comparison of intramuscular analgesic activity of butorphanol and morphine in patients with sickle cell disease. *Ann Emerg Med*. 1988;17:788-791.
31. 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;47:334-340.
32. 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(3). https://doi.org/10.4172/2155-6148.1000394
33. Lubega FA, DeSilva MS, Munube D, et al. Low dose ketamine versus morphine for acute severe vaso occlusive pain in children: a randomized controlled trial. *Scand J Pain*. 2018;18:19-27.
34. Alshahrani MS, Asonto LP, El Tahan MR, et al. Study protocol for a randomized, blinded, controlled trial of ketamine for acute painful crisis of sickle cell disease. *Trials*. 2019;20:286. https://doi.org/10.1186/s13063-019-3394
35. The Joint Commission. Sentinel event alert 11: high alert medications and patient safety. 1999. https://www.jointcommission.org/resources/patient-safety-topics/sentinel-event/sentinel-event-alert-newsletters/sentinel-event-alert-issue-11-high-alert-medications-and-patient-safety/. Accessed March 15, 2021.
36. Dupont W & Plummer W Jr. PS: Power and sample size calculation V3.1.6. 2018. http://biostat.app.vumc.org/wiki/Main/PowerSampleSize. Accessed March 15, 2021.
37. Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70:659-663.
38. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35:549-556.
39. Kissin I, Bright CA, Bradley EL Jr. The effect of ketamine on opioid-induced acute tolerance: can it explain reduction of opioid consumption with ketamine-opioid analgesic combinations? *Anesth Analg*. 2000;91:1483-1488.
40. 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;26:163-167.
41. Chu A, Golembiewski J, Molokie RE. Low-dose ketamine infusion in adult patients with sickle cell disease–impact on management of acute painful episodes. *Am Soc Hematol*. 2013;122:2249.
42. 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:e7-e9.
43. Motov S, Rokoff B, Cohen V, et al. Intravenous subdissociative-dose ketamine versus morphine for analgesia in the emergency department: a randomized controlled trial. *Ann Emerg Med*. 2015;66:222-229.e1. https://doi.org/10.1016/j.annemergmed.2015.03.004
44. Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. *Anesth Analg*. 2003;96:789-795.
45. Jennings CA, Bobb BT, Noreika DM, Coyne PJ. Oral ketamine for sickle cell crisis pain refractory to opioids. *J Pain Palliat Care Pharmacother*. 2013;27:150-154.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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