Otieno DO, Khainga SO, Wanjeri JK, Mwiti TM, Sulemanji DS. Effectiveness of Intravenous Low-Dose Ketamine Versus Morphine for Procedural Burn Pain Management During Dressing Changes: A Randomized Clinical Trial. J Anesthesiol & Pain Therapy. 2024;5(1):6-12

Journal of Anesthesiology and Pain Therapy

Research Article Open Access

Effectiveness of Intravenous Low-Dose Ketamine Versus Morphine for Procedural Burn Pain Management During Dressing Changes: A Randomized Clinical Trial

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Article Info

Article Notes
Received: February 29, 2024
Accepted: April 15, 2024

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Keywords
Low-dose intravenous ketamine
Burn dressing changes
Procedural burn pain management

Abstract

Background: There is limited literature on using low-dose intravenous ketamine as a single agent for procedural burn pain management during adult dressing changes.

Aims & Objectives: To determine the effectiveness of low-dose ketamine compared to morphine as a single analgesic agent in procedural burn pain management during dressing changes.

Materials & Methods: We performed an institutional review board-approved, randomized, prospective, double-blinded, controlled, non-inferiority trial. All adult patients 18 years and above scheduled for dressing change were screened. Patients who consented were randomized to receive low-dose ketamine infusion at 0.2mg/kg/hr. In the treatment group, morphine infusion at 0.1mg/kg/hr. In the control group. The primary endpoint was pain intensity, measured using a visual analog scale. Data were analyzed on an intention-to-treat (ITT) approach. Secondary endpoints included rescue analgesia requirements and the occurrence of adverse effects in both groups.

Results: 82 patients were enrolled (ketamine 41 vs. morphine 41). We compared VAS scores at 5-minute intervals during the dressing changes. Overall, pain scores are similar in both groups (p-value=0.595). The pain control was homogenous. However, the morphine group required more rescue analgesia throughout the dressing changes than the low-dose ketamine group (p=0.013 at T15, p<0.001 at T20, and p<0.001 at T30). The occurrence of side effects was similar in both groups.

Conclusion: This study suggests that low-dose ketamine provides as effective and more predictable procedural analgesia as morphine during dressing procedures for adult burn patients.

Introduction

Burns is a specialized form of trauma with immense severity and disease burden, particularly in Kenya. Severe pain is inevitable owing to burn injuries[1,2]. Burn injuries present a multifaceted problem: physical injury and its sequelae and significant psychological stress, many of which are products of pain[3]. Further to the burden that pain poses for patients with burns, poorly controlled pain has far more complications that deter from a good long-term prognosis. For instance, poorly controlled pain discourages patients from therapeutic interventions such as wound dressing and physiotherapy, resulting in complications such as wound infections, contractures, and venous thromboembolic events due to poor mobility[2].

Procedural pain is often more severe than that caused by the initial injury [i.e., background pain][3]. Procedural pain is underestimated and undertreated, even in specialized burn units[4]. The repercussions of these complications indicate the need for more therapeutic interventions, increased length of hospital stay with increased financial liabilities for patients and healthcare institutions, and, most significantly, a poor long-term prognosis[5,6].

Opioid analgesic agents are the cornerstones of burn pain management[7]. Opioids have drawbacks, such as opioid tolerance and dependence, leading to inadequate pain relief. Ketamine is a widely available and safe anesthetic agent that can be used in various situations. It has analgesic effects at sub-anesthetic doses and has been effective in several clinical cases, even as a single agent for post-operative pain sickle cell pain crises[11], incision and drainage of abscesses, and reduction of fracture-dislocations in the emergency department[8-10,12].

This study aimed to determine the effectiveness of low-dose ketamine compared with morphine as a single agent for procedural burn pain management during burn dressing changes.

Materials and Methods

Study Design

This randomized, controlled, double-blinded, non-inferiority trial was designed to assess the effectiveness of low-dose ketamine and morphine in the procedural pain management of burn patients during dressing changes.

Study Setting

The study was conducted at the Kenyatta National Hospital (KNH) burns unit to guarantee patient safety (anesthesia providers within reach for airway intervention if required). KNH is a national teaching and referral hospital with a total bed capacity of 1800.

Eligibility

Eligible adult patients 18 years and above, with acute major burns, and not endotracheally intubated were screened and recruited. We excluded those with chronic comorbidities (hypertensive, myocardial infarction, and heart failure), psychosis (as acute episodes could be precipitated by ketamine), substance abuse disorder, ketamine allergies, previous ketamine exposure, language barrier, and those that required prone positioning for dressing. Written consent was obtained from all participants.

Sample Size

Power analysis determined that a sample size of at least 41 per group would result in a power of 95%.

Randomization

Randomization was by block randomization with two interventional groups (low-dose ketamine and morphine). An independent statistician used a computer software randomizer (https://www.randomizer.org/) to generate the randomization sequence.

The ketamine group received intravenous ketamine (0.2mg/kg/h), and the morphine group received intravenous (0.1mg/kg/h).

The blinding of participants and study investigators was achieved using 50 cc syringes of similar appearance and consistency. A postgraduate resident in the anesthesia department was recruited to prepare the drug patient per patient according to the allocation. The mixed drug was labeled with the patient study number and delivered to the research assistant using a transparent syringe (all drugs were colorless liquids).

Measures and outcome

The primary endpoint was pain intensity, measured using a visual analog scale. Pain was assessed at baseline (time 0) and then every 5 min until the end of the procedure in an hour or less (time 60). However, only the baseline and last scores at the end of the procedure were scored, and data were analyzed using intention-to-treat (ITT).

The secondary endpoints included rescue analgesia requirements and the occurrence of adverse effects when low-dose ketamine was administered during burn dressing changes.

Study Procedure

Patients who signed the consent were taken to the procedure room. They were handed the validated visual analog scale to record their baseline pain levels (within the last 24 hours). A VAS score of 0 indicated no pain, a score of 1 to 3 indicated mild pain, a score of 4 to 7 indicated moderate pain and a score of 8 to 10 indicated severe pain. After recording their VAS scores, all patients were pre-medicated with glycopyrrolate 0.1 mg iv and midazolam (1 mg).

Low-dose ketamine infusion was administered using a syringe pump (The Infusomat® Space pump). It was prepared as follows: in every 50 cc on a syringe pump, a total of 4 cc ketamine was diluted with 46 cc normal saline, which resulted in a 4 mg/cc solution titrated as appropriate. That way, we were able to use both basal infusion and rescue doses via the infusion pump in a One hour or less of the procedure. Low-dose ketamine was calculated at 0.2 mg/kg/h, whereas morphine was calculated at 0.1 mg/kg/h.

Morphine infusion was constituted as follows: In every 50cc on a syringe pump, a total of 10cc morphine was diluted with 40 cc normal saline, which resulted in a 2 mg/mL solution titrated as appropriate. The infusion preparation was labeled for the patient with a study number from the computer-generated stratification numbers without any other identifying marks in a similar brand transparent calibrated 50cc syringe (all drugs are colorless liquids). The research assistant assigned to the patient commenced the infusion at the same rate of 0.05 ml/kg/h for both the treatment and control groups, which ensured blinding.

Within 5 minutes of the study, drug infusion was initiated, they were handed the visual analog scale again, and dressing changes commenced. During the procedure, patients were asked to give a number every 5 minutes to determine the VAS score and give rescue analgesia to patients with a pain score of 4 and above, defined as breakthrough pain.

Rescue analgesia was titrated to an infusion rate of 0.1 mg/kg/h. until adequate pain control (VAS < 4) or until adverse effects occurred and the dressing procedure was completed. Treatment failure was the inability to achieve adequate pain control during the procedure. These data were documented. Once the procedure was completed, they re-recorded their pain levels using a visual analog scale. The effectiveness of the study drug at this dosage was assessed based on VAS score changes over time during the procedure and the total analgesic dose requirement. The adverse reaction form noted mild to moderate adverse effects such as hypersalivation, emesis, nystagmus, hallucination, and sedation. Severe adverse effects such as respiratory depression, allergic reaction, and cardiac arrhythmia were reported within 24 hours by the institutional review board (IRB). The study drug infusion was stopped for persistent side effects and upon consecutive 15-minute interval measurements of vital signs, recording a heart rate greater than 100 beats per minute, systolic blood pressure less than 90 mmHg, respiratory rate less than ten breaths per minute or greater than 30 breaths per minute, and oxygen saturation of less than 93%.

Data Management

Interviewer-administered questionnaires were used for data collection. The data was cleaned, coded, and analyzed using the Statistical Package for Social Science (SPSS) version 24. The data was explored descriptively using frequency (percentages) and median (Interquartile range) for categorical and continuous variables. The analysis was stratified by study arm (ketamine, morphine) and compared using the chi-square of Fisher's exact test for categorical data and the Wilcoxon rank sum test for the continuous variables. The pain intensity was summarized using the mean (standard deviation). Change in pain intensity calculated by getting the range (max-min) pain intensity and tested for normality assumption using Shapiro Wilk test. All p-values were two-sided, and p-values less than 0.05 were considered to indicate statistical significance.

Results

Eighty-two patients met the eligibility criteria and were recruited into the study, with an equal number of patients in the ketamine and morphine groups. The median age of the participants was 32 years (IQR:26-38), 57 (69.5%) were males, 44 (53.7%) were married, and the median weight was 65 (IQR:62-72) kg, and a median TBSA of 30 (IQR:22-38) percent. (Table 1)

VAS scores

The pain score was monitored before the procedure and every five minutes during the procedure. The mean pain scores are shown in (Figure 1) and show the mean was initially higher for the ketamine group than for the morphine group and reached a peak after 15 min after that, declining below the morphine group. There were no significant differences in the VAS scores between the groups.

The change in VAS scores was calculated for each patient by obtaining the difference between the minimum and maximum values. The Shapiro-Wilk test results showed that

Table 1: Patient's characteristics, N=82

		Study arm		
Characteristic	**Overall, N = 82[1]**	**ketamine, N = 41**	**morphine, N = 41**	**p-value[2]**
Age in years, Median (IQR)	32 (26 – 38)	30 (26 – 36)	32 (26 – 42)	0.68
Gender, n (%)				0.23
Female	25 (30.5)	15 (36.6)	10 (24.4)	
Male	57 (69.5)	26 (63.4)	31 (75.6)	
Marital status, n (%)				0.38
Married	44 (53.7)	20 (48.8)	24 (58.5)	
Single	38 (46.3)	21 (51.2)	17 (41.5)	
Weight (kgs), Median (IQR)	65 (62 – 72)	65 (62 – 72)	65 (63 – 70)	0.95
TBSA (%), Median (IQR)	30 (22 – 38)	30 (21 – 36)	30 (23 – 38)	0.58

[1]Median (IQR); n (%)
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

the normality assumption does not hold (p-value ≤ 0.001) for the overall change and each of the arms. This was also demonstrated using the Q-Q plot (Figure 2) as the points deviated from normality. The difference in the change was tested using the Wilcoxon test with p-value=0.595, which implies no difference in the change in the VAS score between the ketamine and morphine groups. (Table 2)

Rescue Analgesia

The number of patients who received rescue analgesia and the time it was administered was recorded in the ketamine and morphine groups. The two groups differed significantly regarding the need for rescue analgesia at T15, T20, and T30. At T20 and T30, this difference was more pronounced. (Figure 3), (Table 3)

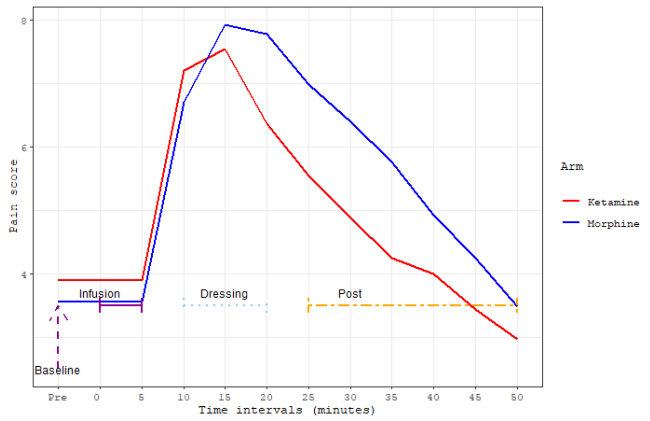

Figure 1: Mean Pain scores at different time points. There were no significant differences regarding VAS scores in either group.

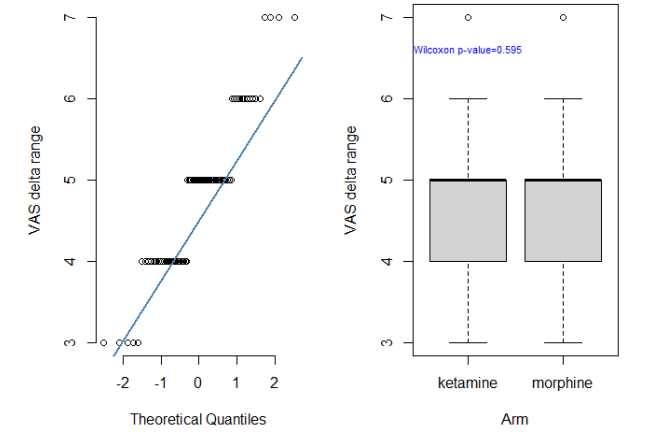

Figure 2: Q-Q Plot and boxplots for change in VAS scores

Table2: At categorical pain levels, perceptions of pain levels were not different between the two groups

VAS score	Ketamine n (%)	Morphine n (%)	P-value
Mild	3 (7.3)	2 (4.9)	0.6444
Moderate	37 (90.2)	36 (87.8)	0.724
Severe	1 (2.4)	3 (7.3)	0.305

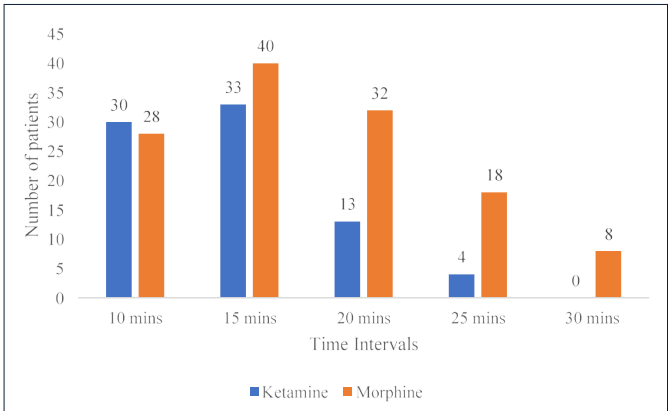

Figure 3: Number of patients on rescue analgesia at any given time intervals

Table 3: Comparison of ketamine and morphine groups concerning rescue analgesia at different time intervals

Time interval	Ketamine n (%)	Morphine n (%)	P-value
10 minutes	30 (73.2)	28 (68.3)	0.240
15 minutes	33 (80.5)	40 (97.6)	0.013
20 minutes	13 (31.7)	32 (78.0)	< 0.001*
25 minutes	9 (9.8)	18 (43.9)	0.255
30 minutes	0 (0.0)	8 (19.5)	< 0.001*

* defines the significant difference

Adverse Effects

The proportion of patients with adverse effects of medication was 22 (26.8%), with nausea, nystagmus, and hallucinations as the most common adverse effects.

Adverse effects such as hallucinations and nystagmus were common in the ketamine group, while nausea was common in the morphine group. No severe adverse effects were observed. However, there was no statistically significant difference between the two groups (Ketamine and morphine group) in age, gender, marital status, weight TBSA, and adverse effects. (Table 4)

Discussion

The main objective of this study was to assess the role of low-dose ketamine as a non-inferior sole analgesic agent in procedural burn pain management during dressing changes at the Kenyatta National Hospital. While most studies report significant benefits of low-dose ketamine as part of combination regimens with opioids and other sedatives or in the pediatric population[13-16], this is the first study to evaluate its role as a single agent in procedural burn pain.

We found that low-dose ketamine was comparable to morphine regarding changes in VAS pain scores from the baseline. Overall, there were no statistically significant differences in the mean pain scores between the low-dose ketamine and morphine groups within 50 min of analgesic administration. Pain in this patient population could be

Table 4: Adverse Effects

		Study arm		
Variable	**Overall, N = 82[1]**	**ketamine, N = 41**	**morphine, N = 41**	**p-value[2]**
Adverse effects, n (%)				0.32
Absent	60 (73.2)	28 (68.3)	32 (78.0)	
Present	22 (26.8)	13 (31.7)	9 (22.0)	
Specific adverse effects, n (%)				
Diaphoresis	1 (4.5)	0 (0.0)	1 (11.1)	0.219
Dysphoria	2 (9.1)	2 (15.4)	0 (0.0)	0.217
Hallucination	4 (18.2)	4 (30.8)	0 (0.0)	0.066
Hiccups	2 (9.1)	1 (7.7)	1 (11.1)	0.784
Lightheaded	2 (9.1)	0 (0.0)	2 (22.2)	0.075
Nausea	5 (22.7)	0 (0.0)	5 (55.6)	0.002*
Nystagmus	5 (22.7)	5 (38.5)	0 (0.0)	0.034*
Thirst	1 (4.5)	1 (7.7)	0 (0.0)	0.394

* defines the significant difference

effectively controlled by both ketamine and morphine. These findings compare well with earlier studies[17,18,19]. In a systematic review and meta-analysis by Balzer et al., low-dose ketamine was an effective alternative to opioids for acute pain in the emergency department. There was no significant difference in the mean pain scores between low-dose ketamine and morphine within the first 60 minutes of analgesia administration[5]. The well-planned analgesic regimen can explain these findings.

Low-dose ketamine was associated with a higher need for rescue analgesics than morphine at T10, which was not statistically significant. The two groups differed significantly regarding the need for rescue analgesia at T15, T20, and T30. At T20 and T30, this difference was more pronounced. These findings are similar to those described by Ashburn et al.[5] but at variance with those of Balzer et al.[20] and Lubega et al.[11] in which the need for rescue was similar in both groups. The explanation for these findings may be multifactorial. This can be explained by the neuropathic component of the pain experience, which is often unresponsive to opioid analgesics[21,22]. Another possible explanation could be that while opioids provide excellent analgesia for most patients with burns[7], opioid tolerance is very likely in burn pain management with higher dose requirements[23]. Our burn patients may have had prior exposure to opioids, necessitating more drug requirements to achieve the same analgesia efficacy despite our strict inclusion criteria for limiting the study to the acute setting. Burn injury induces different drug-specific pharmacokinetic changes that affect blood concentration, resulting in an altered response. Examples of such alterations in drug response in burn patients include tachyphylaxis, which can result in progressively higher doses of the drug to achieve the same level of analgesia[2,24,25]. The volume of distribution is another important parameter that affects patients with burns, either by changes in extracellular volume or protein binding[25]. Burns induce a potent inflammatory response in an acute setting[25]. As a result of the inflammatory response, albumin is downregulated, and alpha-1-acid glycoprotein (AAG) is increased. Therefore, high alpha-1-acid glycoprotein-bound drugs, such as morphine, have reduced serum-free fraction concentrations[25]. This explains the need for dose adjustments in the patient population to achieve the peak effect and steady states. Similarly, the delayed onset of action of morphine[25] can explain the need for repeated dosing of the same drug.

This study also aimed to assess the occurrence of adverse effects when low-dose ketamine was administered compared with morphine during burn dressing changes. The total number of patients who experienced adverse effects was (26.8%). The Ketamine arm recorded nystagmus (12.2%), hallucinations (9.8%), and dysphoria (4.9%) as the most common side effects. Our findings are within the ketamine range[11,13,26-28]. Similarly, nausea (12.2 %), lightheadedness (4.9 %), diaphoresis (2.4 %), and hiccups (2.4 %) were observed in the morphine arm. There was no statistical difference in both arms regarding adverse effects, except for nausea (higher in the morphine arm) and nystagmus (higher in the ketamine arm), as anticipated. The low-dose ketamine group had more adverse effects (31.7%) than the morphine group (22%). However, these differences were not statistically significant. None of the adverse events were life-threatening. These findings are consistent with the literature, which suggests a low-dose ketamine infusion of 0.2 mg/kg/hr. Demonstrates a good analgesic profile and limited side effects[6,29,30]. The use of premedication, such as midazolam and glycopyrrolate, at the beginning of the study may also have contributed to a limited number of adverse effects similar to that described by Balzer et al[20].

These results differ from those of Yousefifard et al.'s study[15], in which ketamine alone had fewer side effects than morphine alone, and the difference was statistically significant.

Our study had several limitations. In this study, we did not interfere with the background (round-the-clock) analgesia plan for which we collected data. The limitation was that the background analgesia plan needed to be standardized as different background analgesic regimens have varying analgesic efficacy and this could affect the observed effects of the trial medications, which will affect the strength of comparability. We had a relatively small sample size (82 patients) due to limited logistic resources, which may limit the generalizability of the findings. Larger sample sizes would provide more statistical power and allow for subgroup analyses to explore potential differences in treatment efficacy among different patient populations. Furthermore, potential sources of bias, such as the lack of blinding among healthcare providers administering the interventions. Health care providers may have predetermined assumptions about the efficacy of either of the drugs and this could have influenced the administration of rescue analgesia. We could have benefited from the longer follow-up duration of the study, which would have allowed us to analyze the side effects of repeated doses or prolonged use of the study drug infusion. However, we did not have a follow-up period after the procedure because of the limited logistics resources.

Despite these limitations, pain control during burn dressing changes using low-dose ketamine as a single agent is not inferior to morphine. The findings of this study suggest that ketamine is more predictable in achieving analgesia than morphine.

This knowledge is essential for policymaking to guide the development of analgesic plans in burn centers. This will improve surgical outcomes, long-term prognosis, and patient satisfaction. We recommend a pain scoring system to help patients objectively define their pain. This is a useful clinical indicator that can be used to guide individual analgesic plans. Further studies with more extended follow-up periods are warranted. This will help to establish the number of patients who still report pain or develop side effects after the initial encounter and cessation of the study drug infusion.

Declarations

Acknowledgments

I wish to acknowledge the role played in the generation, conduct, and finalization of this project by my supervisors: Professor Stanely Khainga, Dr. Joseph Kimani Wanjeri, Dr. Timothy Murithi Mwiti & Dr. Demet Sulemanji. Your guidance and overall insights have made this inspiring for me. Further, I would like to thank Mr. James Orwa & Dr. Idris Chikophe, who helped with the statistics. I am also thankful to my family and friends for all their unconditional support in this intense training. I am grateful to God for the good health and well-being necessary to complete this work.

Conflict of interest

No conflict of interest to declare.

Research Funding

This research received no specific grant from funding agencies in public, commercial, or not-for-profit sectors.

Informed Consent

Written consent was obtained from all participants.

Ethical Approval

This study was approved by the Department of Plastic Surgery (UON) and a KNH Ethics and Research Committee. The approval number is P379/05/20201. The approval period is 5th November 2021- 4th November 2022.

Author Contributions

Dr. Daniel, hand in hand with my supervisors, developed this idea from conceptualization to final proposal. Drs Wanjeri, Mwiti & Demet supervised proposal development and oversaw study design, results interpretation, and manuscript review.

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