Journal of Advances in Medicine and Medical Research

Volume 35, Issue 13, Page 53-66, 2023; Article no.JAMMR.99528
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Oral Morphine versus Rectal Ketamine in Pain Management during Burn Wound Dressing: An Open Label Randomized Clinical Trial

Alice Gertrude Atai [a], Kwikiriza Andrew [a], Okelue Edwards Okobi [b*], Queen Lutina-Oloom Ekpa [c], Oghenekevwe Ekrebe [d], Mercy Oyeinbrakemi Koroyin [e], Anthony I. Dick [f], Kafayat Oluwatoyin Bolaji [g], Enoobong Aderonke Adedoye [h], Aisha M. T. Abubakar [i], Emeka Kenneth Okobi [j] and Endurance O. Evbayekha [k]

[a] Mbarara University of Science and Technology, Mbarara, Uganda.
[b] Larkin Palms Spring Community Hospital, Miami, FL, USA.
[c] Conestoga College, Kitchener, ON, Canada.
[d] University of Port Harcourt, River State, Nigeria.
[e] Crimean Federal University, Republic of Crimea, Russia.
[f] Chicago State University, Chicago, Illinois, USA.
[g] Aminu Kano Teaching Hospital, Kano, Nigeria.
[h] Mater Dei University Teaching Hospital, Msida, Malta.
[i] University of Maiduguri, Nigeria.
[j] Ahmedu Bello University Teaching Hospital, Zaria, Nigeria.
[k] St. Luke's Hospital, Chesterfield, USA.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2023/v35i135045

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/99528

**Corresponding author: E-mail: Drokelue.e.okobi@gmail.com;*

Original Research Article

Received: 25/02/2023
Accepted: 28/04/2023
Published: 09/05/2023

ABSTRACT

Background: Oral morphine has been widely used to manage children's pain during burn wound dressing. Rectal ketamine may also be safely administered to children.
Objective: To evaluate and compare the efficacy of oral morphine vs. rectal racemic ketamine in management of pain during burn wound dressing in a pediatric population in a rural study population.
Methods: This was a randomized open-label clinical trial done in a rural hospital in Uganda. Study participants were randomly assigned to one of the treatment groups, either oral morphine or rectal ketamine, with a ratio of 1:1. Overall, we enrolled 44 participants, with 22 in each treatment arm.
Assessment of baseline vital signs, including pulse rate, blood pressure, respiratory rate, temperature, oxygen saturation (SPO2), pain assessment (using Face Legs Activity Cry Consolability [FLACC]), and sedation scores (using Richmond's agitation and sedation scale [RASS]) among others was done. Study participants were followed up hourly for 8 hours for outcomes of interest: adequate pain management/adverse events.
Results: The mean age of the study participants was 2.56 (±1.59) years. The overall mean intra-procedural pain difference score for children who received oral morphine was 2.7 (SD±2.2) compared to 0 (SD±0) among those who received rectal ketamine, and the mean difference of 2.7 was statistically significant ($p < 0.0001$). Sialorrhea (hyper-salivation) was the only significant adverse event, with more occurrence in the rectal Ketamine treatment arm (n= 8, 36.3%) compared to 1 (5%) in the oral Morphine treatment arm, $p = 0.009$. There were no significant adverse effects noted in either treatment arm.
Conclusion: The study showed the non-inferiority of rectal ketamine over oral morphine and concluded that administration of rectal ketamine was better at pain management and safety compared to oral morphine. Rectal ketamine is associated with an increased incidence of sialorrhea compared to oral morphine.

Keywords: Efficacy; rectal ketamine; oral morphine; pain control; pain management during burn wound dressing; pain management; burn pain management; pediatric pain management; pain; burn; anesthesiology.

1. INTRODUCTION

Burn wounds contribute significantly to surgical disease, morbidity, and mortality burden. A retrospective study of SQUAD data (Surgical services Quality Assurance Database) in this rural hospital showed that most admitted burn patients were children, about 54% under five years old [1]. Many of these burns are potentially curable and occur in the young population. Expanding procedural burn care capacity is essential to decrease in-hospital mortality, pain, and distress strongly associated with burn wound dressing in the pediatric population.

Pain management in pediatrics remains challenging, as inadequately treated pain can lead to more extended hospital stays, higher costs, and lower patient satisfaction [2]. Children suffer pain the same way as adults, although assessing pain in young children can be challenging. Self-reporting is only possible in older children or those with considerable cognitive and communicative abilities. Frequently, factors such as fear, anxiety, coping style, and lack of social support can further exaggerate the physical pain in children [3,4].

In addition, this inadequate pain management may have a long-term psychological impact on the child and the guardian(s), affecting future relationships with healthcare. Generally, in the pediatric population, acute pain management involves using opioids, non-steroidal anti inflammatory agents, and regional analgesics alone or in combination with other drugs. Opioids, including morphine, have been widely used in pain management among children with

moderate to severe acute pain [5]. The use of opioids for pain control should be avoided if possible due to acute opioid tolerance, hyperalgesia [3-6], and adverse effects, not excluding ventilatory depression, pruritus, postoperative nausea and vomiting (PONV), ileus and urinary retention [7,8]. As a result, various pre-medications have been introduced via various routes, including rectal administrations of midazolam and ketamine [9]. Rectal ketamine has been well-documented during the procedural analog sedation of children and is considered safe and effective [10]. Studies show that when midazolam and rectal racemic-ketamine when administered at safe doses during burn dressing in pediatrics, provide the desired level of pain relief and shorten recovery time, ultimately reducing the need for other rescue sedative drugs [4-10]. The use of rectal ketamine for procedural wound dressing may be cheaper, time-friendly, easily administered by a nurse, less invasive than intravenous or intramuscular routes of administration, and has equally shown effective pain management during burn wound dressing in pediatrics [10].

2. BACKGROUND

Burn injuries are a significant cause of morbidity and mortality worldwide, with a disproportionate burden on resource-limited settings [1]. Pain management is an integral part of burn wound care, as uncontrolled pain can impair wound healing, increase the risk of infection, and negatively impact the psychological well-being of patients [3].

In resource-poor settings, oral morphine and rectal ketamine are two commonly used analgesics for burn pain management [9]. Oral morphine is a potent opioid analgesic that acts on the mu-opioid receptor to alleviate pain [10]. However, it has potential side effects, including respiratory depression, sedation, and constipation. Rectal ketamine, a dissociative anesthetic, works by antagonizing the N-methyl-D-aspartate (NMDA) receptor, leading to analgesia, amnesia, and sedation. Its use is limited by potential side effects such as hallucinations, confusion, and urinary retention.

Several studies have compared the efficacy and safety of oral morphine and rectal ketamine in pain management during burn wound dressing. A randomized controlled trial conducted in a resource-poor setting in Nigeria found that rectal ketamine provided more significant pain relief than oral morphine during burn wound dressing, with a lower incidence of side effects [9]. However, another study conducted in India found that oral morphine provided superior pain relief and was better tolerated by patients than rectal ketamine [1].

Overall, the choice of analgesic for burn pain management should be based on individual patient factors, the resources available, and the setting in which the patient is being treated. Healthcare providers should weigh the benefits and risks of each medication carefully and adjust the dosages accordingly to ensure adequate pain control while minimizing side effects.

2.1 Regenerate Response

This study aimed to compare the efficacy of rectal ketamine versus oral morphine in managing procedural pain during burn wound dressing in pediatric patients. In addition, to compare the incidence of adverse events of rectal ketamine versus oral morphine during wound dressing in pediatric patients at the rural hospital.

3. MATERIALS AND METHODS

The study was conducted as an open-label randomized clinical trial with two arms: Rectal ketamine and oral morphine with a 1:1 allocation ratio. The study population included all children aged six months to 6 years requiring wound dressing for burns and analgesia. The age group was appropriate based on the pain score model (FLACC) used in this study. We talked to all the participants' parents before about our options. However, parents did not have the right to decide what arm to belong.

3.1 Inclusion Criteria

Six-month-to-six-year-old pediatric patients scheduled for at least one burn wound dressing operation at the pediatric unit of Mbarara Regional Referral Hospital.

3.2 Exclusion Criteria

Refusal to consent or assent to participate in the study or parental/guardian declination to consent
Children with anal or rectal pathology.

Children who are already intubated or who need mechanical ventilation in an intensive care unit Children who are allergic to ketamine/ketamine constituents.

After consent was obtained, we applied a simple 1:1 randomization ratio. Patient group assignment was generated using the computer algorithm and placed in sealed envelopes. The envelopes were opened sequentially when an eligible participant was recruited. We considered one event of burn wound dressing with the highest expected pain intensity and at a specified time from injury because of the variability related to the different procedures and time of wound dressing..

Sample size:

The formula for equivalence design in randomized clinical trials, $n_B = (1+1/k)\ [(\sigma\ (z1-\alpha+z1-\beta)/(\ \mu_A - \mu_B-\delta)]^2$ was used to determine the sample size.

- $n_A = kn_B$ = sample size in control arm
- n_B= sample size in interventional arm
- $k= n_A/n_B$ is the matching ratio = 1
- $\mu_A - \mu_B$ = estimated difference in mean reduction in pain scores between patients allocated to control and those in interventional arm = 1.5 points= effect difference.
- σ is standard deviation = 1.7 based on studies.
- α is Type I error = 5% (equivalent to Z= 1.96 for the two-sided test)
- β is Type II error, meaning 1−β1−β is power = 0.84 (equivalent to the power of 80%) preferred as minimum power to achieve the desired goal.
- δ is the testing margin. For the non-superiority design, this was taken as zero. No need for reference to non-inferiority margin as would be needed in the non-inferiority designs.

Therefore, $n_B = (1+1/1) * [1.7*((1.96+0.84)/1.5)]^2$
$n_B = 20$

Adding 10% (20/1-0.10) to the sample size to cater for potential withdrawals and loss to follow-ups, the estimated sample size of 22 patients was estimated for each study arm, that is 22 in Control arm and 22 in the interventional arm. Group A received rectal ketamine with rectal midazolam, while those in group B received oral morphine as the traditional routine standard of care protocols. Participants in group A were administered rectal ketamine (6 mg/Kg) with a rectal nozzle infused via the rectum after scoring baseline pain. Then, about 15 minutes later, just before the start of the procedure, assessment of pain and sedation with other vitals were noted as pre-procedural assessment. Patients received rectal midazolam 0.3mg/kg to minimize the side effect of rectal ketamine. Participants in group B were administered 0.3mg/kg of oral morphine about 60 minutes prior to the beginning of every procedure, oral morphine is administered to allow for its commencement of effect, and a baseline assessment was done before drug administration and repeated at 60 minutes just before the start of the procedure. Measurements were recorded using the Revised FLACC pain score and RASS for sedation scores. Intravenous pethidine was administered for breakthrough analgesia 1mg/kg for those with a FLACC behavioral score above three. Intra-procedurally, participants were continuously monitored for breakthrough pain at every step until the dressing procedure was completed or stopped. The patients' pain was scored 5 minutes before the administration of oral morphine to the control arm pre-procedural and 5 minutes before the administration of rectal ketamine to the interventional arm, and then repeated shortly before the start of the procedure in both treatment arms. Intra-operatively, patients were continuously monitored for any breakthrough pain and/or at every step of the procedure until the dressing procedure was completed or stopped.

Finally, postprocedural follow-up of the pain score was done every hour for 8 hours. All the adverse effects were recorded based on the DAIDS Grading system and reported accordingly to the MUST-REC and the data safety monitoring committee charter. We did not record any deaths as SAE, and all patients recovered fully and were transitioned from acute care to the appropriate wound care plan. Other parameters that were recorded included age, weight, duration of the procedure, days since burn injury, the initial intervention, recovery time, type of trauma, the total area burned, the total amount of supplementary pethidine given, blood pressures, pulses rate, oxygen saturation and if the patient required oxygen or not. Research assistants completed the questionnaire. These were registered nurses by profession recruited and trained for data collection in this study.

The primary endpoint was the difference in pain scores in the two arms. Pain score, the

dependent variable in this study, was measured using the FLACC behavioral pain score. The instrument had five categories. Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability; is scored from 0 to 2, resulting in a total score of 0 to 10. The higher the score, the greater the pain. The patient's pain was scored prior to, during the procedure- and every hour post-procedurally for the 8-hour follow-up period. Adequate pain management was defined as a revised FLACC pain score of < 4.

The secondary endpoint was the difference in adverse effects across both arms. Data collected from the case report forms was coded; the entry was done using Microsoft Excel and then imported into STATA 15 (College Station, Texas, USA) for data cleaning and analysis.

Descriptive data were analyzed as means and standard deviations (SD) for continuous variables (age and clinical parameters) and percentages for categorical data. We used the Student t-test to compare means for continuous variables. The Chi-square test (X2) or Fischer's exact test was used where appropriate to compare categorical variables between the treatment arms.

For objective 1: We compared mean pain scores for procedural pain management between the two treatment arms using box and whisker plots and Student t-test statistics. The statistical significance level was $p < 0.05$.

For Objective 2: Fischer's exact test was used to compare the incidence of the adverse effects of rectal ketamine and oral morphine in all the treatment groups.

The statistical significance level was $p < 0.05$.

The clinical trial was also registered at clinical trial.org. NCT05163366. Adverse effects encountered during the study were to be reported to the MUST-REC and the data safety monitoring charter in Uganda through adverse event reporting as part of the pharmacovigilance plan. During the study, codes were used instead of names to foster confidentiality. The participant code number and not the participant's name identified the information. Guardians of patients or their eligible caretakers signed an informed consent form before participating in the study.

4. RESULTS

Study participants were recruited from January 2021 to July 2022. During this study period, 49 participants, aged 6 months to 6 years, were admitted for burn wound dressing, of which five declined to consent to participate in the study. We, therefore, enrolled 44 participants. The mean age of the study participants was 2.56 (±1.59) years. There was no significant difference in participant characteristics by the treatment arm (see Table 1 below).

4.1 Comparison of Pain Scores for Intra-procedural Pain Management in all Treatment Groups

The overall mean intra-procedural pain difference score for children who received morphine was 2.7 (SD±2.2) compared to 0 (SD±0) among those who received rectal ketamine; with a mean difference of 2.7, $p < 0.0001$ (See Fig. 1 below).

4.2 Comparison of Intraoperative Sedation Scores among the Treatment arms

The mean intraoperative Richmoid Agitation and Sedation Scores (RASS) for children who received morphine was 0. (SD±1.31) compared to -2.82 (SD±1.53) among those who received rectal ketamine; with a mean difference of 2.82, $p < 0.0001$ (See Fig. 2 below).

4.3 Comparison of Pre-procedural, Intra-procedural and Average Post-Procedural Pain among Patients with Burn Wounds

There was only a significant difference in the intra-procedural pain scores in the 2 treatment arms, with an average pain score of 2.73 (±2.23) in the oral morphine arm compared to 0 (±0) in the rectal ketamine arm (Mean difference =2.73, $p<0.001$) (See Fig. 3 below). There was no significant difference in the treatment groups' pre-procedural and post-procedural pain scores.

4.4 Comparison of Pre-procedural, Intra-procedural, and Average post-Procedural Pain among Children with Burn Wounds (N = 44)

There was no significant difference in the treatment groups' pre-procedural and post-procedural pain scores (See Table 2 below).

Table 1. Socio-demographic and clinical characteristics (N =44) and clinical parameters of study participants. (SD= Standard Deviation)

Variables		Total (N=44)	Control	Intervention	P-value
			Oral Morphine (N=22)	Rectal Ketamine (n=22)	
		n/N (%)	n/N (%)	n/N (%)	
Age in years (Mean±SD)		2.56 (±1.59)	2.83 (±1.76)	2.22 (±1.32)	0.200
Age categories (years)	< 3 years	27(61.36)	13 (48%)	9 (53%)	0.757
	≥3 years	17(38.64)	14 (52%)	8 (47%)	
Gender	Male	30 (68.2)	18 (82.0)	12 (54.5)	0.052
	Female	14 (38.6)	4 (18.0)	10 (45.5)	
Caretaker	Guardian	6 (13.6)	3 (13.0)	3 (14.3)	0.23
	Parent	38 (86.4)	20 (87.0)	18 (85.7)	
Type of trauma	Scalding	36 (81.8)	17 (77.3)	19 (86.4)	0.430
	Flame burns	8 (18.2)	5 (22.7)	3 (13.6)	
Total burn surface area (%)	<10% (mild)	11(25.0)	4(18.2)	7(31.8)	0.140
	≥10%	33(75.0)	15(68.2)	18(81.8)	

Clinical parameters of study participant

Clinical characteristics	Total (N=44)	Control	Intervention	P-value
		Morphine (N=22)	Rectal Ketamine (n=22)	
	(Mean±SD)	(Mean±SD)	(Mean±SD)	
Pre-procedural heart rate (bpm)	137.3 (±23.1)	136.8 (±21.0)	137.8 (±25.5)	0.320
Post-procedural heart rate (bpm)	111.9 (±18.0)	111.4 (±14.9)	112.4(±20.9)	0.581
Pre-procedural systolic BP (mmHg)	98.9(±12.1)	102(±12.2)	95.8 (±11.4)	0.910
Post-procedural systolic BP (mmHg)	90.6(±13.5)	89.7(±15.3)	91.5(±11.9)	0.111
Pre-procedural diastolic BP (mmHg)	67.6(±11.9)	69.9 (±14.5)	65.2(±13.5)	0.960
Post-procedural diastolic BP (mmHg)	60.0(±13.5)	58.2(±17.0)	61.7(±13.5)	0.871
Pre-procedural respiratory rate (bpm)	28.3(±9.0)	29.9(±11.4)	26.8(±5.6)	0.613
Postprocedural respiratory rate (bpm)	23.9(±3.6)	23.9(±3.7)	23.8((±3.6)	0.351
Pre-procedural oxygen saturation (%)	94.6(±3.9)	96.1(±4.3)	94.1(±3.7)	0.010
Post-procedural oxygen saturation (%)	97.3(±2.9)	96.9(±3.6)	97.7(±1.9)	0.334
Pre-procedural temperature (^{o}C)	37.2(±1.1)	37.4(±0.9)	37.1(±1.2)	0.351
Post-procedural temperature (^{o}C)	37.4(±0.7)	37.5(±0.8)	37.2(±0.5)	0.229

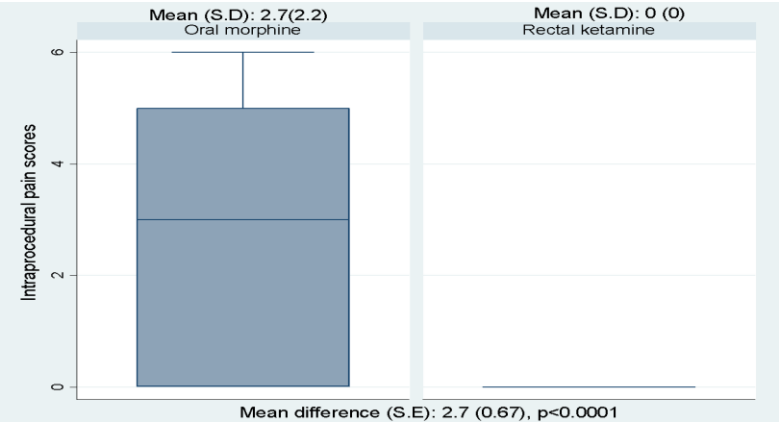

Fig. 1. Comparison of pain scores for intra-procedural pain management in all treatment groups

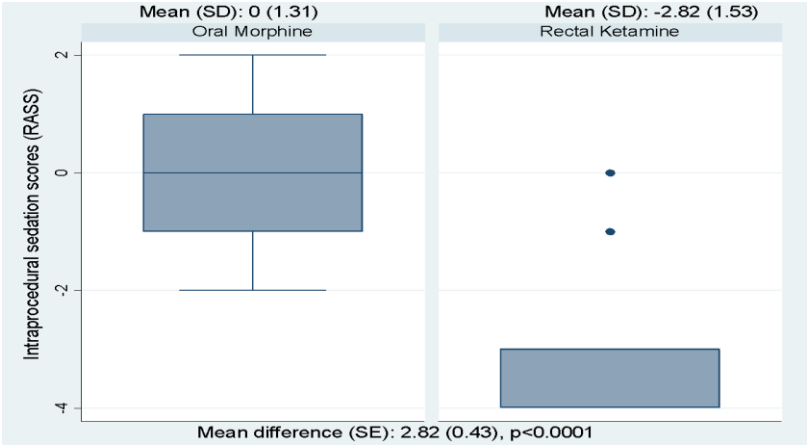

Fig. 2. Comparison of intraoperative sedation scores among the treatment arms

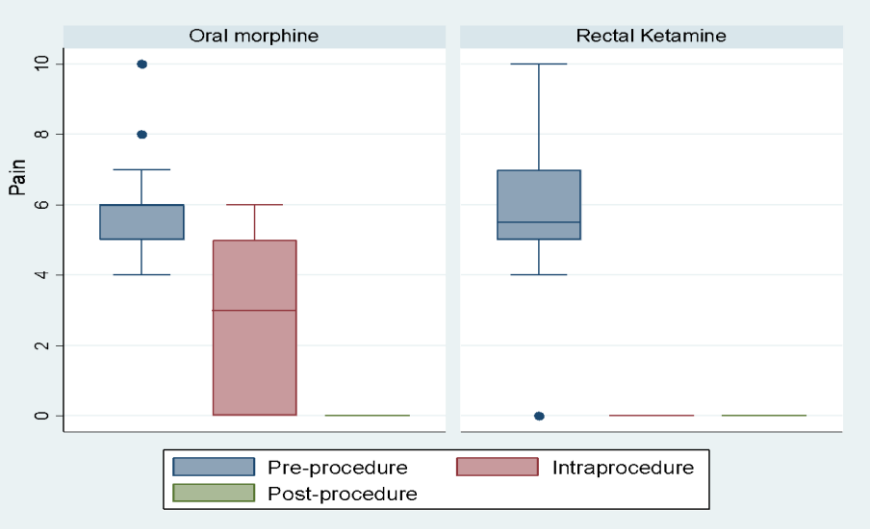

Fig. 3. Comparison of pre-procedural, intra-procedural and average post-procedural pain among patients with burn wounds

Table 2. Comparison of pre-procedural, intra-procedural, and average post-procedural pain among children with burn wounds (N = 44)

	Total	Oral morphine	Rectal ketamine	Mean difference	p-value
	N=44	N=22	N=22		
		Mean (±SD)	Mean (±SD)		
Pre-procedural pain score	6.09 (1.83)	6.14 (1.36)	6.05 (2.24)	0.09	0.871
Intra-procedural pain score	1.36 (2.08)	2.73 (2.23)	0 (0)	2.73	<0.001*
Post-procedural pain score		0 (0)	0 (0)		-

*****$p < .05$

Table 3. Comparison of the incidence of adverse events by treatment arm for rectal ketamine versus oral morphine

			Control	Intervention	
		Total	Oral morphine	Rectal ketamine	p-value
		N=44	N=22	N=22	
		n/N (%)	n/N (%)	n/N (%)	
Nausea	No	42 (95%)	20 (91%)	21 (95%)	0.55
	Yes	3 (6.8%)	2 (9%)	1 (5%)	
Vomiting	No	39 (89%)	20 (91%)	19 (86%)	0.63
	Yes	5 (11%)	2 (9%)	3 (14%)	
Hyper-salivation	No	35 (80%)	21 (95%)	14 (64%)	0.009*
	Yes	9 (20%)	1 (5%)	8 (36%)	
Respiratory depression	No	44 (100%)	22 (100%)	22 (100%)	
	Yes	0 (0%)	0 (0%)	0 (0%)	
Delayed recovery	No	35 (80%)	17 (77%)	18 (82%)	0.711
	Yes	9 (20%)	5 (23%)	4 (18%)	
Desaturation	No	33 (77%)	16 (76%)	17 (77%)	0.932
	Yes	10 (23%)	5 (24%)	5 (23%)	
Bradycardia	No	43 (98%)	21 (95%)	22 (100%)	0.310
	Yes	1 (2%)	1 (5%)	0 (0%)	
Tachycardia	No	41 (93%)	19 (86%)	22 (100%)	0.073
	Yes	3 (7%)	3 (14%)	0 (0%)	
Need for Rescue Analgesia	No	33 (75%)	14 (64%)	19 (86%)	0.082
	Yes	11 (25%)	8 (36%)	3 (14%)	
Oxygen requirement	No	34 (77%)	16 (73%)	18 (82%)	0.471
	Yes	10 (23%)	6 (27%)	4 (18%)	
Propofol administration	No	44 (100%)	22 (100%)	22 (100%)	
	Yes	0 (0%)	0 (0%)	0 (0%)	
Halothane administration	No	44 (100%)	22 (100%)	22 (100%)	
	Yes	0 (0%)	0 (0%)	0 (0%)	
Non rebreathing	No	43 (98%)	21 (95%)	22 (100%)	0.312
	Yes	1 (2%)	1 (5%)	0 (0%)	
Intubated	No	44 (100%)	22 (100%)	22 (100%)	
	Yes	0 (0%)	0 (0%)	0 (0%)	

			Control	Intervention	
		Total	Oral morphine	Rectal ketamine	p-value
		N=44	N=22	N=22	
		n/N (%)	n/N (%)	n/N (%)	
Follow up variables					
Nausea	No	43 (98%)	21 (95%)	22 (100%)	0.310
	Yes	1 (2%)	1 (5%)	0 (0%)	
Vomiting	No	37 (84%)	18 (82%)	19 (86%)	0.680
	Yes	7 (16%)	4 (18%)	3 (14%)	
DIB (difficult in breathing)	No	44 (100%)	22 (100%)	22 (100%)	
	Yes	0	0	0	
Hyper-salivation	No	39 (89%)	22 (100%)	17 (77%)	0.018*
	Yes	5 (11%)	0 (0%)	5 (23%)	
Irritability	No	38 (86%)	20 (91%)	18 (82%)	0.381
	Yes	6 (14%)	2 (9%)	4 (18%)	

4.5 Comparison of the Incidence of Adverse Events by Treatment Arm for Rectal Ketamine Versus oral Morphine

There were significant differences in adverse events (effects) among children in the treatment group in terms of only hyper-salivation. There was no significant difference in occurrence of nausea, vomiting, respiratory depression, tachycardia, irritability, delayed recovery and desaturation. Hyper-salivation was observed more in the rectal ketamine treatment arm (n= 8, 36.3%) compared to 1 (5%) in the morphine treatment arm, p = 0.009 (See Table 3).

5. DISCUSSION

Rectal ketamine offered better pain management than oral morphine. Our findings are consistent with those of a randomized study of rectal ketamine during pediatric burn wound dressing procedures that used midazolam and rectal ketamine (5-10mg/kg) during a pediatric burn wound dressing procedure [9-10]. Ketamine has strong analgesic properties and has been noted to provide an ideal opioid alternative [11-14]. Contrary to our findings, a retrospective case series of 33 children and adolescents found that low-dose ketamine lacked an opioid-sparing effect, with patients receiving Ketamine reporting higher pain scores and requiring higher additional doses of opioids than those receiving only opioids (without ketamine).

This study, however, utilized ketamine at a lower dose (0.1 mg/ kg/h) [15]. Our observed differences are explained by the differences in dose and mode of delivery (intravenous versus oral versus rectal). Our study used rectal ketamine (6 mg/kg) versus oral morphine (0.3mg/kg). The other studies used intravenous or intramuscular formulations of both ketamine and morphine and a low dose of ketamine (0.1 to 1 mg /kg) and morphine (0.1mg). Except for hyper-salivation significantly noted in the rectal ketamine arm, there were no other observed adverse events in this study. Our finding is similar to other studies [16,17]. Similar to other studies [18,19], the occurrence of respiratory depression and hemodynamic instability was not statistically different.

Ketamine is safe, effective, and convenient, with a superior cardiovascular stability profile and tolerable adverse effects and is less likely to cause respiratory depression [11,13,18,19]. The rectal route of administration of ketamine is associated with more minor peak plasma levels of ketamine, resulting in fewer or less pronounced adverse effects than the parenteral route of administration [10,11]. This could have further explained the fewer adverse events observed in our study.

As found in our study, hyper-salivation has been noted as a common side effect of ketamine [20]. We, however, did not observe any other gastrointestinal adverse effects, such as nausea, vomiting, anorexia, and abdominal pain, as noted to be commonly associated with the use of ketamine from other studies unclear [21]. Other studies also noted agitation [16,17], which was not noted in our study. We administered midazolam with rectal ketamine to avoid this phenomenon [22].

Similar study designs have compared other potential options in managing pains from burn wounds such as Dexmedetomidine. Dexmedetomidine is a centrally acting alpha-2 agonist with sedative and analgesic properties that has demonstrated efficacy in managing pain, agitation, and delirium in a variety of settings [23,24]. It has a highly selective α-2 adrenoreceptor agonist activity and functions as a sedative, anxiolytic, and analgesic without any respiratory depressive effects [23,24]. Dexmedetomidine may require monitoring of vital signs, but it is effective in managing pain and sedation in the ICU and operating room [23,24]. It has been shown to be useful in managing pain in cardiac catheterization procedures in pediatric patients. In a study comparing the effects of ketamine-propofol and ketamine-dexmedetomidine combinations on hemodynamic parameters and recovery time in pediatric patients undergoing minor procedures and cardiac catheterization, the ketamine-dexmedetomidine combination was found to be effective [23-24]. When compared with oral morphine, Dexmedetomidine may require monitoring of vital signs, but it has a highly selective α-2 adrenoreceptor agonist activity and functions as a sedative, anxiolytic, and analgesic without any respiratory depressive effects [23,24].

6. CONCLUSIONS

In conclusion, the study showed the non-inferiority of rectal ketamine over oral morphine, and further showed that rectal ketamine may

have a better pain control than oral morphine. However, rectal ketamine had a higher incidence of hyper-salivation compared to oral morphine. Given the safety profile of rectal ketamine and the significant difference in pain control compared to oral morphine, it is reasonable to administer rectal ketamine for analgesic purposes during the routine dressing of burns in children, and also given its advantage of a non-opioid approach without respiratory depression, a real advantage in a rural setting. Therefore, we recommend using ketamine as an alternative to morphine while dressing burn wounds in children. We recommend a multi-centered study for external validity testing of the trial.

7. STUDY LIMITATION

A notable limitation of this study was the use of midazolam in the intervention group that received ketamine. The use of midazolam in the intervention group is a potential confounder and limitation to the study. Midazolam, a notable short-acting benzodiazepine with sedative, anxiolytic, and amnesic effects, is used occasionally to mitigate the side effects of ketamine, such as hallucinations and lucid dreams. To obviate this side effect, midazolam was given. However, midazolam, over the years, has been argued to may or may not have analgesic properties; however, in combination with ketamine, it may augment ketamine's analgesic effect and may have confounded the result of the study. Also, this study was single centered; perhaps a multi-centered trial will increase the sample size given that burns in the pediatric population are non-predictable presentations. Another limitation was that our follow-up time for this study was within 8 hours post-procedure, so we missed out on the late adverse events. Other variables as enzymatic or genetic polymorphism were not considered during this trial.

CONSENT

Guardians or parents of patients scheduled for burn-wound care signed an informed consent form pre-procedurally for both standard of care pain management and study purposes. All participants whose parents or guardians who refused informed consent were not recruited for the study.

ETHICAL APPROVAL

The clinical trial received approval from the Research Ethical Committee (REC) of Mbarara University of Science and Technology.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Nakitto M, Lett R: Paediatric burn injuries: a hospital based study in Uganda . Injury Prevention. 2010;16:46-47.
   Available:https://doi.org/10.1136/ip.2010.029215.169
2. Shipton EA: The transition of acute postoperative pain to chronic pain: Part 1 - Risk factors for the development of postoperative acute persistent pain. Trends in Anaesthesia and Critical Care. 2014;4:67-70.
   Available:https://doi.org/10.1016/j.tacc.2014.04.001
3. Li LQ, Wang C, Xu HY, Lu HL, Zhang HZ. Effects of different doses of intranasal dexmedetomidine onpreoperative sedation and postoperative agitation in pediatric with total intravenous anesthesia undergoing adenoidectomy with or without tonsillectomy. Medicine. 2018, 97:12140.
   Available:https://doi.org/10.1097/md.0000000000012140
4. O'Rourke D. The measurement of pain in Infants, children, and adolescents: from policy to practice .Physical Therapy. 2004;84.
   Available:https://doi.org/10.1093/ptj/84.6.560
5. Rosen DM, Alcock MM, Palmer GM. Opioids for acute pain management in children . Anaesthesia and Intensive Care. 2022;50:81-94.
   Available:https://doi.org/10.1177/0310057X211065769
6. Guignard B, Bossard AE, Coste C, et al.: Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology. 2000;93:409-417.
   Available:https://doi.org/10.1097/00000542-200008000-00019

7. Oderda GM, Evans RScott, Lloyd J, et al. Cost of opioid-related adverse drug events in surgical patients. Journal of Pain and Symptom Management. 2003;25: 276-283.
   Available:https://doi.org/10.1016/s0885-3924(02)00691-7
8. O'Donnell FT, Rosen KR. Pediatric pain management: a review. Missouri medicine. 2014;111(3): 231-237.
   Accessed. Accessed: January 18, 2023: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6179554/ .
9. Tanaka M, Sato M, Saito A, Nishikawa T: Reevaluation of Rectal Ketamine Premedication in Children. Anesthesiology. 2000;93:1217-1224.
   Available:https://doi.org/10.1097/00000542-200011000-00014
10. Pedraz JL, Calvo MB, Lanao JM, Muriel C, Lamas JS, Dominguez-GIL A. Pharmacokinetics of rectal ketamine in children. British Journal of Anaesthesia. 1989, 63:671-674.
    Available:https://doi.org/10.1093/bja/63.6.671
11. Grossmann B, Nilsson A, Sjöberg F, Nilsson L. Rectal ketamine during paediatric burn wound dressing procedures: A randomised dose-finding study. Burns. 2019:45:1081-1088.
    Available:https://doi.org/10.1016/j.burns.2018.12.012
12. Porter SB, Schwenk ES: Ketamine and remote hyperalgesia. Minerva Anestesiologica. 2018;84.
    Available:https://doi.org/10.23736/s0375-9393.18.12521-1
13. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American society of regional anesthesia and pain medicine. Reg Anesth Pain Med. 2018;45:1.
    Available:https://doi.org/10.1097/aap.0000000000000806
14. Edrich T, Friedrich AD, Eltzschig HK, Felbinger TW: Ketamine for long-term sedation and analgesia of a burn patient. Anesthesia and Analgesia. 2004;99: 893-895.
    Available:https://doi.org/10.1213/01.ane.0000133002.42742.92
15. Neri C, Pestieau S, Young H, Elmi A, Finkel J, Neri C: The George Washington University Health Sciences Research Commons Pediatrics Faculty Publications Pediatrics. 2014. Accessed January 18; 2023.
16. Tran K, Nguyen Q, Truong XN, et al. A comparison of ketamine and morphine analgesia in prehospital trauma care: A cluster randomized clinical trial in rural Quang Tri province, Vietnam. Prehosp Emerg Care. 2014:18:257-264.
    Available:https://doi.org/10.3109/10903127.2013.851307
17. Johansson P, Kongstad P, Johansson A: The effect of combined treatment with morphine sulphate and low dose ketamine in a prehospital setting. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2009;17:61.
    Available:https://doi.org/10.1186/1757-7241-17-61
18. Maldini B. Ketamine anesthesia in children with acute burns and scalds. Acta Anaesthesiologica Scandinavica. 1996;40: 1108-1111.
    Available:https://doi.org/10.1111/j.1399-6576.1996.tb05572.x
19. Ward CM, Diamond AW An appraisal of ketamine in the dressing of burns . Postgraduate Medical Journal. 1976;52: 222-223.
    Available:https://doi.org/10.1136/pgmj.52.606.222
20. Orhurhu VJ, Vashisht R, Claus LE, Cohen SP: Ketamine Toxicity. Pub Med. Published. 2022, Accessed: January 17, 2023:
    Available:https://pubmed.ncbi.nlm.nih.gov/31082131/
21. Klepstad P, Borchgrevink PC. Four years' treatment with ketamine and a trial of dextromethorphan in a patient with severe post-herpetic neuralgiaActa Anaesthesiologica Scandinavica. 1997;41: 422-426.
    Available:https://doi.org/10.1111/j.1399-6576.1997.tb04709.x
22. Craven R. Ketamine: Anaesthesia. 2007;62:48-53.
    Available:https://doi.org/10.1111/j.1365-2044.2007.05298.x
23. Anger K. Dexmedetomidine: A review of its use for the management of pain, agitation,

and delirium in the Intensive care unit. Current Pharmaceutical Design. 2013; 19(22):4003-4013.
DOI:https://doi.org/10.2174/1381612811319220009

24. Joshi V, Kollu S, Sharma R. Comparison of dexmedetomidine and ketamine versus propofol and ketamine for procedural sedation in children undergoing minor cardiac procedures in cardiac catheterization laboratory. Annals of Cardiac Anaesthesia. 2017;20(4):422.
DOI:https://doi.org/10.4103/aca.aca_16_ 17

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/99528