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ORIGINAL RESEARCH

The Efficacy and Safety of an RN-Driven Ketamine Protocol for Adjunctive Analgesia During Burn Wound Care

Findings indicate that adjunctive low-dose ketamine was safe and provided pain relief.

Burn-related pain is severe and often difficult to manage. Health care providers struggle to achieve adequate control of such pain, especially when it's invoked by wound care management procedures such as dressing changes.[1-3] Because burn patients often require high doses of opioids and anxiolytics, clinicians must weigh the risks of oversedation against the need to achieve adequate analgesia and anxiolysis. Inadequate pain control during these procedures has been associated with increased pain perception, anxiety, and fear surrounding the experience, which in turn may play a role in depression, acute stress disorder, and posttraumatic stress disorder (PTSD).[1,4,5] Other therapeutic options for better management of pain and anxiety during burn wound care procedures remain to be identified.

The mechanism of evoked pain during burn wound care is not fully understood. That said, there is some evidence linking such pain to sensitization of the central nervous system[6] and specifically to the excitability of the N-methyl-D-aspartate (NMDA) receptor pathway.[7] (NMDA is an amino acid derivative that influences how the body reacts to excitatory stimuli.) Ketamine, a phencyclidine derivative, produces analgesia and event dissociation by inhibiting the binding of glutamate to the NMDA receptor; it also enhances the analgesic effects of opioids, thus helping to prevent opioid tolerance.[8] Given that ketamine antagonizes NMDA receptors, it's possible it could be effective in managing pain during burn wound care. Moreover, although consensus is lacking, there is some evidence that ketamine has minimal effects on a patient's respiratory drive and hemodynamic profile.[9-12] Thus ketamine might be an ideal analgesic for patients in hypovolemic states, such as occurs in trauma and large-volume burns. But there are also concerns. Ketamine has been associated with adverse effects, including hallucinations,[11,13] vivid dreams,[11-13] agitation and anxiety,[13] and nausea and vomiting.[11-13]

Several studies have found that the addition of low-dose ketamine to traditional analgesic combinations is effective in maintaining patient comfort during postoperative and trauma wound care (including burns), and can minimize the need for large doses of opioids and anxiolytics.[11,14,15] But in most studies, physicians—most commonly anesthesiologists—supervised the administration of ketamine. The goal of this study was to assess the efficacy and safety of a practice protocol allowing critical care RNs to independently administer ketamine for burn wound care. The hypothesis was that this protocol would reduce patients' opioid and anxiolytic requirements for pain management without affecting patient safety.

METHODS

Design, setting, and sample. This was a retrospective cohort study conducted in a 12-bed burn ICU at a large academic medical center in Colorado. The

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ABSTRACT

Objective: Traditional analgesic regimens often fail to control the severe pain patients experience during burn wound care, and the drugs are frequently administered at doses that can cause oversedation and respiratory depression. Ketamine may be an ideal agent for adjunctive analgesia in such patients because of its unique mechanism of action and lack of association with respiratory depression. This study evaluated the efficacy and safety of a critical care RN–driven protocol for IV ketamine administration during burn wound care.

Methods: This retrospective cohort study examined all adult burn patients who received ketamine as part of a critical care RN–driven ketamine protocol for burn wound care from September 2011 through September 2013. Efficacy outcomes were opioid and benzodiazepine requirements (expressed as fentanyl and midazolam equivalents, respectively) four hours after ketamine administration compared with four hours before such administration. Safety parameters assessed were neurologic, hemodynamic, and respiratory effects.

Results: Twenty-seven patients received 56 ketamine doses as part of this protocol; the mean (SD) dose was 0.75 (0.35) mg/kg. Twenty patients (74%) were male and seven (26%) were female; mean age was 39 years. The average percentage of total body surface area burned was 23.4%. With the protocol, opioid and benzodiazepine requirements were reduced by 29% and 20%, respectively. One patient experienced an episode of oversedation after concomitant administration of ketamine and fentanyl. No patients experienced neurologic or hemodynamic complications following ketamine administration.

Conclusions: The administration of ketamine during burn wound care using a critical care RN–driven protocol was associated with reduced opioid and benzodiazepine requirements and few adverse effects. Prospective studies are needed to investigate additional patient outcomes and the independent administration of ketamine by critical care RNs.

Keywords: analgesia, burn wound care, critical care, ketamine, RN-driven protocol, pain

organization's institutional review board approved the protocol before data collection began. Patient consent and Health Insurance Portability and Accountability Act approval were not required. All adult burn patients between the ages of 18 and 89 were considered if they were identified as having an order for ketamine as part of the critical care RN–driven ketamine protocol for burn wound care between September 1, 2011, and September 30, 2013. Patients were so identified by searching the pharmacy database for the protocol-specific number. Patients were excluded if they had received ketamine for reasons other than burn wound care.

The protocol, which was developed by a multidisciplinary team that included nurses, burn ICU physicians, anesthesiologists, and pharmacists, was created for the use of critical care RNs practicing in the burn ICU. Before implementation, it was approved by the organization's Nursing Practice Guidelines Subcommittee and Burn Process Improvement Committee. Critical care RNs completed an intensive one-day, on-site training that was directed by nurse managers, burn ICU physicians, and anesthesiologists. The training included both didactic education and skills assessment, and encompassed drug administration, documentation and monitoring, patient safety, patient-specific scenarios, and emergency management. State regulations regarding RN scope of practice were followed. Providers authorized to order the protocol included physicians certified in conscious sedation, critical care, or both; pain service advanced NPs; and anesthesiologists. A pharmacist verified that each ketamine order was appropriate before it was released to the critical care RN for administration. Once the ketamine protocol was ordered, its use was at the discretion of the critical care RN, based on her or his perception that a patient was in discomfort or was requiring such high doses of opioids that safety was a concern. (For detailed information on the protocol, contact the lead author.)

Data collection. Data were extracted and maintained in an Excel spreadsheet in a deidentified format. The following variables were collected: age, sex, height, weight, history of alcohol or substance abuse, medical history and comorbidities, admission diagnosis, other hospital diagnoses, total body surface area (TBSA) burned, length of ICU stay, laboratory values on the day ketamine was administered, ketamine dosage and time of administration, dosages of all analgesics and anxiolytics given during the four hours before and after ketamine administration, other medicines administered during that time period, type and duration of wound care, vital signs (temperature, heart rate, respiratory rate, and blood pressure) taken

every 15 minutes during the hour before and after ketamine administration, oxygen requirements during dressing changes, and notes indicating the occurrence of an adverse event following ketamine administration (hypo- or hypertension, tachycardia, hallucinations, vivid dreams, agitation or anxiety, nausea and vomiting, excessive sedation). Given that pain scores and delirium scores weren't consistently documented pre- and post-dressing changes, Richmond Agitation–Sedation Scale (RASS) scores were collected for four hours before and after ketamine administration and used to assess overall patient discomfort. (See *The Richmond Agitation–Sedation Scale*.[16])

The primary efficacy outcomes were the patient's requirements for opioids and benzodiazepines during the four hours following ketamine administration compared with the four hours beforehand. Opioid and benzodiazepine requirements were expressed as fentanyl and midazolam equivalents, respectively. IV hydromorphone and morphine were converted to fentanyl equivalents using standard conversion values (hydromorphone 1.5 mg IV = morphine 10 mg IV = fentanyl 100 mcg IV). IV lorazepam was converted to midazolam equivalents using the standard conversion value (lorazepam 0.5 mg IV = midazolam 1 mg IV).

The secondary outcomes were safety outcomes; these included changes in systolic blood pressure, heart rate, respiratory rate, oxygen requirements, and the presence of the aforementioned adverse events following ketamine administration. Hypotension was defined as a systolic blood pressure of 90 mmHg or less, or a decrease in systolic blood pressure of 40 mmHg or more. Hypertension was defined as a systolic blood pressure of 180 mmHg or greater, or an increase in systolic blood pressure of 40 mmHg or more. Tachycardia was defined as a heart rate of 120 beats per minute or higher, or an increase in heart rate of 20 beats per minute or more. Agitation was defined as having a RASS score of +2 to +4 within four hours of ketamine administration; oversedation was defined as having a RASS score of –3 to –5 within the same time period.

Statistical analysis. Because this study was retrospective, a power analysis was not conducted. Based on the experience of the team's burn physicians, it was estimated that data on 25 subjects representing at least 50 ketamine doses would be available. Parametric data were reported as means and proportions were expressed as percentages. Pre- and post-ketamine administration comparisons—changes in opioid and benzodiazepine requirements, systolic blood pressure, heart rate, and respiratory rate—were assessed using the paired Student *t* test or the Wilcoxon rank-sum test. Statistical analysis was performed using JMP, version 10 (SAS Institute).

RESULTS

Twenty-seven patients received 56 doses of IV ketamine per the critical care RN–driven ketamine protocol for burn wound care (see Table 1 for patient characteristics). Twenty patients (74%) were male and seven (26%) were female; their mean age was 39 years. The average (SD) percentage of TBSA burned was 23.4% (16.9%). Nineteen patients (70.4%) had TBSA burns greater than 10% with both torso and limb involvement, and eight patients (29.6%) had TBSA burns less than 10% with only limb involvement. With the protocol, opioid and benzodiazepine requirements were reduced by 29% and 20%, respectively. The mean (SD) ketamine dose administered during a single wound care session was 0.75 (0.35) mg/kg, with a minimum dose of 0.18 mg/kg and a maximum dose of 1.4 mg/kg. Each wound care session lasted an average of 74 minutes (range, 49 to 99). All but one dose of ketamine was preceded by the recommended dose of midazolam. No patients were on mechanical ventilation during protocol use.

Patients' opioid and benzodiazepine requirements during burn wound care in the four hours following ketamine administration were significantly reduced (see Table 2). Regarding vital signs, compared with values taken every 15 minutes in the hour before

The Richmond Agitation–Sedation Scale[16]

The Richmond Agitation–Sedation Scale (RASS) is a 10-point scale for assessing levels of agitation and sedation in hospitalized patients. It has demonstrated high validity and reliability; and, according to researchers, nurses have described it as "logical, easy to administer, and readily recalled."

The tool can be administered in a minute or less. It involves up to three steps: observation, assessing response to auditory stimulation (a loud voice), and assessing response to physical stimulation (the patient's shoulder is shaken, and if unresponsive, the sternum is rubbed). The patient's level of agitation is scored between 0 and +4, with 0 representing "alert and calm," and +4 representing "combative." The level of sedation is scored between –1 and –5, with –1 representing "drowsy" and –5 representing "unarousable." Complete instructions for administering the RASS are readily found online and are also in the cited reference by Sessler and colleagues.

ketamine administration, there were no statistically significant changes in systolic blood pressure, heart rate, or respiratory rate at 15, 30, and 45 minutes following ketamine administration (see Table 3). No cases of hypo- or hypertension, tachycardia, hallucinations, vivid dreams, agitation or anxiety, or nausea and vomiting were noted. RASS scores and oxygen requirements after ketamine administration were similar to those measured beforehand. One patient experienced respiratory depression from oversedation that immediately followed the concurrent administration of fentanyl 100 mcg and ketamine 0.6 mg/kg. The patient received naloxone and responded appropriately; no further intervention was needed.

DISCUSSION

This study found that ketamine administration led to significant reductions in patients' opioid and benzodiazepine requirements during burn wound care. Although pain scores weren't recorded in patient charts during burn wound care, RASS scores indicated that agitation and discomfort were not evident after ketamine was administered. This suggests that adjunctive ketamine provided comfort while reducing the need for opioids and benzodiazepines.

Ketamine administration via the critical care RN–driven protocol appears to be safe. There were no changes in patients' hemodynamic profiles following ketamine administration, and there were no occurrences of hallucinations, vivid dreams, agitation or anxiety, or nausea and vomiting. A single dose of a benzodiazepine immediately before ketamine administration may help reduce the likelihood of these adverse effects. As per the protocol, midazolam was administered before all but one of the ketamine doses. Although one episode of oversedation leading to respiratory depression occurred, it immediately followed the concurrent administration of fentanyl and ketamine, and was reversed with naloxone, an opioid antagonist.

It's well known that the high doses of opioids and anxiolytics often required for pain control during burn wound care can have significant adverse short- and long-term effects. Adverse short-term effects include respiratory depression, hypotension, brady- or tachycardia, and increased sedation. In our experience, another short-term effect is prolonged hospitalization, associated with difficulty in maintaining pain control when transitioning from high-dose IV to oral medications. Long-term consequences include tolerance, requiring higher doses of medications to maintain comfort, and an increased risk of physical dependence. In this study, a further concern was that nearly 50% of patients had substance abuse issues prior to hospitalization, which could increase the risk of continued substance abuse.

Despite receiving the large doses of opioids and anxiolytics often administered during burn wound care, patients have reported that evoked pain—the pain associated with procedural dressing changes—is moderate to high,[17] with some reporting it's "the worst possible pain imaginable."[18] Indeed, one qualitative study found that this pain caused fear, psychological "scarring," and reluctance to participate in physiotherapy.[18] As noted earlier, the mechanism of evoked pain during burn wound care isn't fully understood. That said, it appears that burn injuries initiate an inflammatory cascade that sensitizes the nociceptors at the site of injury to mechanical stimulation, including touch, debridement, and other essential aspects of dressing changes and subsequent wound care.[6, 19] Further stimulation of these nociceptors increases central nervous system excitability through the NMDA receptor pathway, leading to secondary

Table 1. Patient Characteristics (N = 27)

Characteristics	Values
Sex, n (%)	
Male	20 (74.1)
Female	7 (25.9)
Mean age, years (SD)	38.9 (12.5)
Average TBSA burned, % (SD)	23.4 (16.9)
Inhalation injury, n (%)	2 (7.4)
Necrotizing soft tissue infection, n (%)	4 (14.8)
History of substance abuse, n (%)	13 (48.1)
• Alcohol abuse	5 (18.5)
• Prescription opioid abuse	5 (18.5)
• Other	3 (11.1)
Burn ICU mean length of stay, days (SD)	34.1 (29.4)

TBSA = total body surface area.

Table 2. Opioid and Benzodiazepine Requirements During Burn Dressing Changes

Medication	4 Hours Pre-Ketamine Administration	4 Hours Post-Ketamine Administration	*P* Value
Fentanyl equivalents, mcg (SD)	471.9 (502.6)	337 (473.8)	< 0.001
Midazolam equivalents, mg (SD)	6.4 (9.5)	5.1 (9.8)	< 0.001

hyperalgesia (pain in the area surrounding the burn site) and further escalation of pain during wound care.[6,20] Thus, given that ketamine antagonizes NMDA receptors, it may help to limit secondary hyperalgesia, but further research is needed.

during burn wound care, but all required physician supervision for ketamine administration.[26-28] Burn wound care, which often involves daily debridement and dressing changes, is time intensive for staff, making it impractical for a physician to be present at all

Patients' opioid and benzodiazepine requirements during burn wound care in the four hours following ketamine administration were significantly reduced.

Analgesic doses of ketamine for procedures have been reported to range from 0.1 to 1.5 mg/kg IV,[21-23] with anesthetic doses ranging from 1 to 4.5 mg/kg IV.[24] By using a standardized adjunctive dose of ketamine in the study protocol (0.5 to 1 mg/kg IV), we sought to maintain the analgesic effects of ketamine while minimizing the unwanted psychotropic side effects that often accompany higher dosages. Kundra and colleagues specifically evaluated the use of oral ketamine (eliminating the need for physician supervision of IV ketamine administration) versus oral dexmedetomidine, a sedative and analgesic.[25] They found that patients in the oral ketamine group had significantly improved pain scores compared with those in the oral dexmedetomidine group. The oral dose given, 5 mg/kg, was higher than what is typically reported, but oral ketamine dosages are usually higher than those used in IV regimens. The researchers did note significant issues with delirium and excessive salivation, although the patients still preferred ketamine.[25] Our study explored the use of IV ketamine; further research might investigate adjunctive ketamine given orally.

Previous studies have found similar results regarding the efficacy of ketamine as an analgesic agent

times. To our knowledge, ours is the first study to evaluate the administration of IV ketamine using a critical care RN–driven protocol during burn wound care, alleviating the need for physician presence. It should be noted that the protocol was developed in accordance with the scope of practice for RNs in Colorado, a state that considers RNs to be independent practitioners; Colorado does not require physician oversight when the dependent nursing function has been delegated by written plan, verbal order, standing order, or protocol. Not all states permit this level of independent nursing practice.

Limitations. The major limitations of this study are the retrospective nature of data collection involving few subjects and the use of the ketamine protocol according to physician and critical care RN discretion. The absence of documented assessments of pain and delirium in the patients' charts prevented us from definitively assessing the effectiveness of ketamine administration. While the reductions in opioid and benzodiazepine requirements following burn wound care and the absence of change in RASS scores offer compelling evidence that ketamine provides effective analgesia, pain scores would be a more appropriate measurement on which to base that conclusion.

Table 3. Systolic Blood Pressure, Heart Rate, and Respiratory Rate During Burn Dressing Changes

Vital Sign	15 Minutes Pre-Ketamine Administration	Post-Ketamine Administration			*P* Value[a]
		15 Minutes	30 Minutes	45 Minutes	
Systolic blood pressure, mmHg (SD)	134 (21.6)	138.8 (20.8)	140 (17.6)	139 (20.9)	NS
Heart rate, beats per minute (SD)	99.2 (18.3)	105 (17.7)	106.5 (19.5)	104.7 (19.2)	NS
Respiratory rate, breaths per minute (SD)	18.2 (5.1)	17.1 (4.9)	18.2 (5)	17.8 (4.5)	NS

NS = not significant.
[a] Post- vs. pre-ketamine administration.

That said, the RASS was chosen as the primary monitoring tool for the protocol because it encompasses both discomfort and oversedation, whereas a pain scale only assesses pain. Furthermore, the study design did not allow us to assess whether the adjunctive use of ketamine, with an expected reduced need for opioids and benzodiazepines, had potential long-term benefits. Prospective studies are needed to further evaluate changes in patients' perception of pain after ketamine administration, and to explore the impact of ketamine use on long-term outcomes such as chronic pain, anxiety, depression, substance abuse, acute stress disorder, and PTSD. Lastly, it must be emphasized that the development of this protocol was feasible given the state's scope of independent practice for RNs, which may not be applicable in other states.

CONCLUSIONS

The administration of low-dose IV ketamine using a critical care RN–driven protocol was associated with reduced opioid and benzodiazepine requirements, with few adverse effects. The protocol also maximized the capabilities of these nurses, empowering them in the care of their patients. Additional prospective studies will help further validate the safety and efficacy of a critical care RN–administered ketamine protocol. A better understanding of the mechanism of evoked pain during burn wound care will be essential to identifying effective interventions; further research in this area is also needed. ▼

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REFERENCES

1. Patterson DR, et al. Pain management. *Burns* 2004;30(8):A10-A15.
2. Richardson P, Mustard L. The management of pain in the burns unit. *Burns* 2009;35(7):921-36.
3. Summer GJ, et al. Burn injury pain: the continuing challenge. *J Pain* 2007;8(7):533-48.
4. McKibben JB, et al. Acute stress disorder and posttraumatic stress disorder: a prospective study of prevalence, course, and predictors in a sample with major burn injuries. *J Burn Care Res* 2008;29(1):22-35.
5. Taal LA, Faber AW. Post-traumatic stress, pain and anxiety in adult burn victims. *Burns* 1997;23(7-8):545-9.
6. Pedersen JL, Kehlet H. Secondary hyperalgesia to heat stimuli after burn injury in man. *Pain* 1998;76(3):377-84.
7. Petrenko AB, et al. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg* 2003;97(4):1108-16.
8. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). *CNS Neurosci Ther* 2013;19(6):370-80.
9. Richards JR, Rockford RE. Low-dose ketamine analgesia: patient and physician experience in the ED. *Am J Emerg Med* 2013;31(2):390-4.
10. Sih K, et al. Ketamine in adult emergency medicine: controversies and recent advances. *Ann Pharmacother* 2011;45(12):1525-34.
11. Subramaniam K, et al. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesth Analg* 2004;99(2):482-95.
12. Visser E, Schug SA. The role of ketamine in pain management. *Biomed Pharmacother* 2006;60(7):341-8.
13. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. *Anesth Analg* 2003;97(6):1730-9.
14. Bredmose PP, et al. Pre-hospital use of ketamine for analgesia and procedural sedation. *Emerg Med J* 2009;26(1):62-4.
15. McGuinness SK, et al. A systematic review of ketamine as an analgesic agent in adult burn injuries. *Pain Med* 2011;12(10):1551-8.
16. Sessler CN, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166(10):1338-44.
17. Weinberg K, et al. Pain and anxiety with burn dressing changes: patient self-report. *J Burn Care Rehabil* 2000;21(2):157-61.
18. Yuxiang L, et al. Burn patients' experience of pain management: a qualitative study. *Burns* 2012;38(2):180-6.
19. Laycock H, et al. Peripheral mechanisms of burn injury-associated pain. *Eur J Pharmacol* 2013;716(1-3):169-78.
20. Ali Z, et al. Secondary hyperalgesia to mechanical but not heat stimuli following a capsaicin injection in hairy skin. *Pain* 1996;68(2-3):401-11.
21. American College of Emergency Physicians, Emergency Medicine Practice Committee. *Sub-dissociative ketamine for analgesia: policy resource and education paper*. Irving, TX 2017 Oct. Policy resource and education papers; https://www.acep.org/globalassets/new-pdfs/preps/prep---sub-dissociative-dose-ketamine-for-analgesia-120717.pdf.
22. Lexicomp. *Lexi-drugs. Ketamine*. Wolters Kluwer Clinical Drug Information. n.d. http://www.wolterskluwercdi.com/lexicomp-online.
23. Persson J. Ketamine in pain management. *CNS Neurosci Ther* 2013;19(6):396-402.
24. Par Pharmaceutical. *Ketalar (ketamine hydrochloride) injection CIII*. Chestnut Ridge, NY; 2017 Apr; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/016812s043lbl.pdf.
25. Kundra P, et al. Oral ketamine and dexmedetomidine in adults' burns wound dressing: a randomized double blind cross over study. *Burns* 2013;39(6):1150-6.
26. Canpolat DG, et al. Ketamine-propofol vs ketamine-dexmedetomidine combinations in pediatric patients undergoing burn dressing changes. *J Burn Care Res* 2012;33(6):718-22.
27. Gunduz M, et al. Comparison of effects of ketamine, ketamine-dexmedetomidine and ketamine-midazolam on dressing changes of burn patients. *J Anaesthesiol Clin Pharmacol* 2011;27(2):220-4.
28. Zor F, et al. Pain relief during dressing changes of major adult burns: ideal analgesic combination with ketamine. *Burns* 2010;36(4):501-5.