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Multicenter Retrospective Review of Ketamine Use in the ICU.

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OBSERVATIONAL STUDY

OPEN

Multicenter Retrospective Review of Ketamine Use in the ICU

IMPORTANCE: The response of ICU patients to continuously infused ketamine when it is used for analgesia and/or sedation remains poorly established.

OBJECTIVES: To describe continuous infusion (CI) ketamine use in critically ill patients, including indications, dose and duration, adverse effects, patient outcomes, time in goal pain/sedation score range, exposure to analgesics/sedatives, and delirium.

DESIGN, SETTING, AND PARTICIPANTS: Multicenter, retrospective, observational study from twenty-five diverse institutions in the United States. Patients receiving CI ketamine between January 2014 and December 2017.

MAIN OUTCOMES AND MEASURES: Chart review evaluating institutional and patient demographics, ketamine indication, dose, administration, and adverse effects. Pain/sedation scores, cumulative doses of sedatives and analgesics, and delirium screenings in the 24 hours prior to ketamine were compared with those at 0–24 hours and 25–48 hours after.

RESULTS: A total of 390 patients were included (median age, 54.5 yr; interquartile range, 39–65 yr; 61% males). Primary ICU types were medical (35.3%), surgical (23.3%), and trauma (17.7%). Most common indications were analgesia/sedation (n = 357, 91.5%). Starting doses were 0.2 mg/kg/hr (0.1–0.5 mg/kg/hr) and continued for 1.6 days (0.6–2.9 d). Hemodynamics in the first 4 hours after ketamine were variable (hypertension 24.0%, hypotension 23.5%, tachycardia 19.5%, bradycardia 2.3%); other adverse effects were minimal. Compared with 24 hours prior, there was a significant increase in proportion of time spent within goal pain score after ketamine initiation (24 hr prior: 68.9% [66.7–72.6%], 0–24 hr: 78.6% [74.3–82.5%], 25–48 hr: 80.3% [74.6–84.3%]; $p < 0.001$) and time spent within goal sedation score (24 hr prior: 57.1% [52.5–60.0%], 0–24 hr: 64.1% [60.7–67.2%], 25–48 hr: 68.9% [65.5–79.5%]; $p < 0.001$). There was also a significant reduction in IV morphine (mg) equivalents (24 hr prior: 120 [25–400], 0–24 hr: 118 [10–363], 25–48 hr: 80 [5–328]; $p < 0.005$), midazolam (mg) equivalents (24 hr prior: 11 [4–67], 0–24 hr: 6 [0–68], 25–48 hr: 3 [0–57]; $p < 0.001$), propofol (mg) (24 hr prior: 942 [223–4,018], 0–24 hr: 160 [0–2,776], 25–48 hr: 0 [0–1,859]; $p < 0.001$), and dexmedetomidine (µg) (24 hr prior: 1,025 [276–1,925], 0–24 hr: 285 [0–1,283], 25–48 hr: 0 [0–826]; $p < 0.001$). There was no difference in proportion of time spent positive for delirium (24 hr prior: 43.0% [17.0–47.0%], 0–24 hr: 39.5% [27.0–43.8%], 25–48 hr: 0% [0–43.7%]; $p = 0.233$). Limitations to these data include lack of a comparator group, potential for confounders and selection bias, and varying pain and sedation practices that may have changed since completion of the study.

CONCLUSIONS AND RELEVANCE: There is variability in the use of CI ketamine. Hemodynamic instability was the most common adverse effect. In the 48 hours after ketamine initiation compared with the 24 hours prior, proportion of time spent in goal pain/sedation score range increased and exposure to other analgesics/sedatives decreased.

KEY WORDS: analgesia; delirium; drug-related side effects and adverse reactions; hypnotics and sedatives; intensive care units; ketamine

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Ketamine is a rapid-acting anesthetic agent originally developed in the 1960s for induction of anesthesia. Antagonism of the N-methyl-D-aspartate receptor produces analgesia at low doses (≤ 0.5 mg/kg/hr) and amnesia and unresponsiveness without suppressing spontaneous respirations or involuntary limb movement at higher doses (≥ 1 mg/kg/hr) (1). Ketamine also possesses activity at opioid, monoaminergic, cholinergic, nicotinic, and muscarinic receptors, which may result in increased blood pressure, heart rate (HR), and cardiac output, bronchodilation, and antidepressant and anti-inflammatory effects (1–3). This unique pharmacology combined with a relatively low acquisition cost has led to increased use for a wide variety of off-label indications in the ICU (4–12).

Unfortunately, there is limited research available to guide use of continuous infusion (CI) ketamine in the ICU. The 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU suggest using low-dose ketamine (0.5 mg/kg × 1 followed by a 1–2 µg/kg/min CI) as an adjunct to opioid therapy when seeking to reduce opioid consumption in postsurgical adults admitted to the ICU (conditional recommendation, very low quality of evidence) (13). They do not address use of ketamine as a sedative agent; therefore, specific recommendations related to its prescribing and monitoring remain absent (13). These guidelines do recommend to optimize analgesia first with a multimodal analgesic approach, followed by light sedation using either propofol or dexmedetomidine (13). However, critically ill patients often have barriers to implementing these strategies, including contraindications to nonopioid analgesics, dose-limiting adverse effects, and/or failure of conventional therapy particularly when deep sedation is necessary. Ketamine may be an ideal benzodiazepine sparing option in these situations; however, its comparative effects on delirium and other risks are unknown.

This study sought to describe use of CI ketamine in critically ill patients, including indications, dose and duration, adverse effects, patient outcomes, proportion of time in goal pain/sedation score range, exposure to analgesics/sedatives, and delirium. We hypothesized after CI ketamine initiation, proportion of time spent in goal pain and sedation score range would increase, cumulative exposure to other analgesic and sedative agents would decrease, and proportion of time spent positive for delirium would decrease.

MATERIALS AND METHODS

Study Setting and Design

This was a multicenter, retrospective, observational study of adult patients who received CI ketamine while admitted to an ICU between January 2014 and December 2017. The primary objective was to describe CI ketamine indications, dose, and duration of therapy. Secondary objectives were to determine the occurrence rate of adverse effects, proportion of time spent in goal pain and sedation score range, cumulative doses of analgesics and sedatives, proportion of time spent positive for delirium, and describe patient outcomes.

The study was designed and executed by members of the Ketamine-ICU study group, who were recruited through the American College of Clinical Pharmacy (ACCP) Practice-Based Research Network (now the ACCP Foundation). Additional sites were recruited to participate from the ACCP Critical Care Practice and Research Network via electronic mail and targeted contact by investigators. All study sites received approval for conduct of this study with waivers of informed consent from their Institutional Review Boards (IRBs). Each site was listed within the IRB approval from University of Rochester Office for Human Subject Protection (STUDY00001686), which functioned as the coordinating site. The guidelines for reporting observational studies with the Strengthening the Reporting of Observational Studies in Epidemiology checklist was used to strengthen the reporting of our findings.

Patient Population

Patients were included if greater than or equal to 18 years old and received CI ketamine for any duration of time while in an ICU during the study time frame and excluded only if transferred in from an outside hospital already receiving CI ketamine. Due to the large amount of data points collected, participating sites were instructed to collect data on as many patients as they could during the data collection timeframe starting with the most recent patients first.

Data Collection and Outcomes

Standardized data collection was performed in a secure Research Electronic Data Capture (REDCap) database. The data collection tool was developed, tested, and refined for ease of use and standardization by the Ketamine-ICU study group. Prior to the study start date, all sites independently reviewed and tested the REDCap tool, reviewed the data dictionary, and participated in a conference call hosted by the coordinating site.

Data collection included both institutional and patient demographics (**Methods**, Supplemental Digital Content, http://links.lww.com/CCX/A910). Data collected for CI ketamine included initial ketamine indication, bolus doses and infusion rate, titration instructions, CI concentration, daily minimum and maximum infusion rates, cumulative doses up to day 7 of therapy, and total duration of therapy.

Data points collected to evaluate for adverse effects included the presence of hypertension, hypotension, tachycardia, bradycardia, or any cardiac abnormalities in the first 4, 24, and 48 hours after CI ketamine initiation. Systolic blood pressure (SBP), mean arterial pressure (MAP), and HR were compared in the 4 hours prior to and 4 hours after CI ketamine initiation. These time frames were chosen to limit the potential for confounders but also describe hemodynamic changes commonly seen during the first few days of therapy. Additional adverse effects that could be dose-related or occur at any time point during therapy such as seizures, hypertonia, hypersalivation, and emergence, allergic, and injection site reactions were collected during the first 7 days of CI ketamine or until ketamine was discontinued, whichever occurred first. Definitions of adverse effect endpoints can be found in Supplemental Digital Content (**Table S1**, http://links.lww.com/CCX/A910).

Data collected to describe CI ketamine analgesia and sedation practices in patients receiving ketamine for an analgesia or sedation indication included baseline oral/IV analgesic, sedative, and antipsychotic use in the 24 hours prior to ketamine including epidural use. Total cumulative doses of IV analgesics (opioids) and sedatives (benzodiazepines, propofol, dexmedetomidine) given in the 24 hours prior to ketamine were compared with cumulative doses given in the first 0–24 hours and 25–48 hours of the infusion. Cumulative doses of opioids and benzodiazepines were converted to IV morphine equivalents in mg (fentanyl 100 μg = hydromorphone 1.5 mg = morphine 10 mg) and midazolam equivalents in mg (lorazepam 1 mg = diazepam 5 mg = midazolam 2 mg), respectively (14, 15). Antipsychotic use was collected in all patients during the first 7 days of CI ketamine or until the infusion was discontinued, whichever occurred first.

To determine the proportion of time spent in goal pain/sedation score range, all pain and sedation scores recorded in the 24 hours prior to CI ketamine initiation were compared with those recorded in the first 0–24 hours and 25–48 hours of the infusion for those receiving CI ketamine for a pain or sedation indication. Goal pain and sedation scores were determined by medical chart review and, if unknown, goal pain scores were assumed to be equivalent to scores indicating no pain to mild pain (Nonverbal Pain Scale 0–3, Behavioral Pain Scale 3–5, Critical Care Pain Observational Tool 0–2, Numerical Rating Pain Scale 0–2, Multidimensional Objective Pain Assessment Tool 1–3, Defense and Veterans Pain Rating Scale of 0–2, Pain Assessment in Advanced Dementia Scale 1–3, Wong-Baker Faces Pain Rating Scale 0–2) and sedation scores were assumed to be equivalent to scores indicating light sedation (Richmond Agitation-Sedation Scale [RASS] −2 to 0 or Sedation Agitation Scale [SAS] 3–4). Similarly, to determine the proportion of time spent positive for delirium, all delirium screenings recorded in the 24 hours prior to CI ketamine initiation were compared with those recorded in the first 0–24 hours and 25–48 hours of the infusion in all patients. The proportion of delirium screenings positive for delirium were collected for the first 7 days of the infusion or until the infusion was discontinued, whichever occurred first. To measure pain and sedation endpoints, the scale used, the score, time the score was taken, and whether the score was in the goal range were collected. Similarly, the delirium screening tool, positive or negative result, time the screening was taken, and whether the patient was able to be screened for delirium based on their level of consciousness (SAS > 2, RASS > −2) were collected for the delirium endpoints.

Patient outcomes evaluated in all patients were ICU and hospital length of stay, 28-day ventilator-free days, discharge disposition, and mortality.

Statistical Analysis

Data were evaluated using SAS software (Version [9.4], copyright © [2016]; SAS Institute, Cary, NC) and SigmaPlot 14 software (Systat, San Jose, CA) and reported using descriptive statistics with mean and SD or median and interquartile range, as appropriate. Continuous data were compared with Student's *t* test, Wilcoxon rank-sum test, one-way analysis of variance (ANOVA), or Kruskal-Wallis test by ranks depending on number of groups and data distribution. Before-and-after data were compared with paired *t* tests, signed rank-sum, or repeated measures ANOVA on ranks. Differences in hemodynamics and cardiac abnormalities were assessed using Cochran's Q test.

Median values were used for comparison of integer-based scoring systems (e.g., SAS, RASS). As various different pain and sedation scales were used between institutions, collected values were categorized and evaluated as proportion of time within goal based on institution-specific or patient-specific goals at the time of data collection.

Reported drug doses suspected to be erroneous (falling outside of three SDs from the mean) were excluded from the analysis given concerns for data entry error suspected due to the varying dosing units observed in practice. A sensitivity analysis was conducted to confirm that removal of these values did not change the outcome. While the amount of data removed varied due to different numbers of patients on each agent, less than 2.5% of data points were removed overall.

RESULTS

Institution and Study Population Demographics

Twenty-five geographically diverse institutions were included. Patient numbers by institution can be found in Supplemental Digital Content (**Table S2**, http://links.lww.com/CCX/A910). These were moderate to large institutions with most having clinical practice guidelines for managing pain and agitation (*n* = 18, 72%), however, very few included ketamine (*n* = 5/18, 27.8%). Several institutions had separate guidelines for ketamine use that included many indications in addition to pain/agitation (*n* = 17, 68%). Further details on institution demographics, pain, agitation, and delirium assessment tools and ketamine practices are available in Supplemental Digital Content (**Tables S3** and **S4**, http://links.lww.com/CCX/A910).

There were 390 adult patients evaluated with a median age of 54.5 years (39–65 yr) and majority were male (61%). Most were located in an ICU at the time of CI ketamine initiation (*n* = 362, 92.8%) and the primary ICU types were medical (35.3%), surgical (23.3%), and trauma (17.7%). Admitting diagnoses were variable but were mostly for trauma (23.8%), respiratory failure (22.1%), postsurgical care (11.5%), and shock (10.5%). The study population was reflective of a moderate to severely ill patient cohort with a median Acute Physiology and Chronic Health Evaluation II score of 21 (14–27), 310 (79%) on mechanical ventilation, 132 (33.9%) on vasopressor therapy, and 36 (9.2%) on CI neuromuscular blocking agents. Additional patient demographics and admitting diagnoses are available in **Table 1** and Supplemental Digital Content (**Tables S5** and **S6**, http://links.lww.com/CCX/A910).

Ketamine Indication, Dose, and Duration

The primary indications for CI ketamine were sedation (*n* = 170, 44%), analgesia (*n* = 115, 29%), and analgosedation (when used for both analgesia and sedation) (*n* = 72, 20%). Other indications included status epilepticus (*n* = 14. 3.6%), bronchodilation (*n* = 10, 2.6%), substance withdrawal (*n* = 5 1.3%), suicidality/antidepressant (*n* = 1, 0.3%), increased intracranial pressure (*n* = 1, 0.3%), and unknown (*n* = 2, 0.5%) (**Fig. 1**, Supplemental Digital Content, http://links.lww.com/CCX/A910). Ketamine was used for pain most commonly in the surgical and trauma ICU patient population, whereas it was used for sedation and analgosedation mostly in the medical ICU population. Ketamine was more commonly used as an adjunctive (*n* = 247, 69%) rather than standalone agent (*n* = 110, 31%). The reason ketamine was chosen could not be explained by any allergies, intolerances, or clinical failure of traditional sedative agents as the majority (*n* = 365, 93.6%) reported this information was unavailable. At baseline, (*n* = 265, 75%) of patients were on a CI analgesic or sedative, (*n* = 169, 48.1%) were on adjunctive nonopioid analgesics and sedatives, and (*n* = 11, 3.1%) had an epidural. Not all patients were on opioids (opioid use: 58.7% infusions, 25.1% scheduled intermittent doses, 79.8% as needed doses). Additional information on baseline analgesic, sedative, and antipsychotic use can be found in the Supplemental Digital Content (**Table S7**, http://links.lww.com/CCX/A910).

TABLE 1.
Baseline Demographics for Patients Receiving Continuous Infusion Ketamine (*n* = 390)

Demographics	Value
Weight, kg, mean ± SD (*n* = 313)	90.8 ± 27.7
Height, inches, mean ± SD (*n* = 260)	67.1 ± 4.4
Ethnicity, *n* (%)	
Non-Hispanic	318 (81.5)
Hispanic	26 (6.7)
Other/not reported	46 (11.8)
Race, *n* (%)	
White	244 (62.6)
Black/African American	64 (16.4)
Other	7 (1.7)
Unknown	75 (19.2)
Primary ICU type, *n* (%)	
Medical	138 (35.3)
Surgical	91 (23.3)
Trauma	69 (17.7)
Cardiovascular	36 (9.2)
Neuroscience	29 (7.4)
Combined medical/surgical	17 (4.4)
Burn	6 (1.5)
Post-anesthesia	2 (0.5)
Pediatric	1 (0.3)
Transplant	1 (0.3)
Hospital location at time of ketamine initiation, *n* (%)	
ICU	362 (92.8)
Emergency department	17 (4.4)
Progressive care/step-down	5 (1.3)
Operating room	5 (1.3)
Post-anesthesia care unit	1 (0.3)
Mechanical ventilation, *n* (%)	310 (79.5)
Ketamine initiated prior to intubation	27 (8.7)
Ketamine discontinued after extubation	47 (15.2)

The CI ketamine dose, dose units, and duration varied and are found in **Table 2**. Only 25% of patients received an initial bolus dose and the majority received weight-based CI doses in either μg/kg/min (60.0%) or mg/kg/hr (33.9%) with actual body weight used in 80.8%

TABLE 2.
Continuous Infusion Ketamine Dose and Administration (*n* = 390)

Dose Information	Value
Loading dose	
Dose, mg/kg, median (IQR), *n* = 99	0.9 (0.4–1.0)
Weight, kg, median (IQR)	82.7 (70.0–101.1)
Weight used, *n* (%)	
Actual	80 (80.8)
Estimated	12 (12.1)
Ideal	4 (4.0)
Adjusted	3 (3.0)
Continuous infusion	
Initial units, *n* (%)	
μg/kg/min	234 (60.0)
mg/kg/hr	132 (33.9)
mg/hr	24 (6.1)
Initial dose[a], median (IQR)	
Overall	0.2 (0.1–0.5)
Analgesia	0.15 (0.09–0.3)
Analgosedation	0.2 (0.12–0.3)
Sedation	0.3 (0.12–0.5)
Alcohol withdrawal	1.2 (1.1–1.25)
Bronchodilation	0.5 (0.08–0.9)
Status epilepticus	0.55 (0.3–1)
Weight, kg, median (IQR), *n* = 366	81.6 (68.0–98.5)
Weight used, *n* (%)	
Actual	300 (82.0)
Ideal	38 (10.4)
Estimated	18 (4.9)
Adjusted	10 (2.7)
Ketamine titratable dose	
Ketamine–titratable CI, *n* (%)	228 (58.5)
Initial rate, dose, median (IQR)	
μg/kg/min (*n* = 176)	2.5 (1.4–5.0)
mg/kg/hr (*n* = 41)	0.2 (0.1–0.5)
mg/hr (*n* = 9)	10.0 (10.0–25.0)
Unknown (*n* = 2)	–[b]
Dose increments, median (IQR), *n* = 228	
μg/kg/min (*n* = 67)	1 (1–5)
mg/kg/hr (*n* = 39)	0.1 (0.1–0.2)
mg/hr (*n* = 8)	5 (5–20)

(*Continued*)

TABLE 2. (*Continued*).
Continuous Infusion Ketamine Dose and Administration (*n* = 390)

Unknown (*n* = 114)	–[b]
Titration endpoints, *n* (%), *n* = 228	
Sedation score	128 (56.1)
Pain score	56 (24.6)
Burst suppression/seizures	3 (1.3)
Incentive spirometry	2 (0.9)
Wheezing	1 (0.4)
Blood pressure	1 (0.4)
Unknown	55 (24.1)
Ketamine fixed dose	
Ketamine–fixed-rate CI, *n* (%)	162 (41.5)
Initial rate, dose, median (IQR)	
μg/kg/min (*n* = 57)	3.0 (1.8–5.5)
mg/kg/hr (*n* = 91)	0.5 (0.2–1.0)
mg/hr (*n* = 14)	25.0 (25.0–33.0)

CI = continuous infusion, IQR = interquartile range.
[a]All doses converted to mg/kg/hr.
[b]Unable to determine value.

of patients. After converting the units to mg/kg/hr, the median initial and discontinuation rates were 0.2 (0.1–0.5) and 0.3 (0.1–0.6), respectively. Median starting doses were greater than or equal to 0.5 mg/kg/hr when used for alcohol withdrawal, bronchodilation, or status epilepticus and less than 0.5 mg/kg/hr when use for pain and agitation. Ketamine infusions were given for a median duration of 1.6 days (0.6–2.9 d). A fixed-rate strategy was used more than a titratable CI (58.5% vs 41.5%). Additional data on daily ketamine cumulative, minimum, and maximum doses and volume infused are available in Supplemental Digital Content (**Table S8**, http://links.lww.com/CCX/A910).

Hemodynamic Changes

Hemodynamic changes before and after CI ketamine were evaluated in 254 patients and were variable. There were no significant differences between median SBP (113.8 mm Hg [100.5–132.5 mm Hg] vs 114.5 mm Hg [102.1–131.0 mm Hg]; p = 0.514), MAP (76 mm Hg [68–88.1 mm Hg] vs 77.5 mm Hg [69.0–86.6 mm Hg]; p = 0.237), and HR (94.3 beats/min [79.5–110.3 beats/min] vs 94.3 beats/min [79.5–110.0 beats/min]; p = 0.781) in the 4 hours before and 4 hours after CI ketamine. During the initial 4 hours of CI ketamine hypertension, hypotension, tachycardia, and bradycardia occurred in 24.0% (n = 53), 23.5% (n = 52), 19.5% (n = 43), and 2.3% (n = 5) of patients, respectively. In the next 5–24 hours, there was a significant increase in the incidence of hypertension (37.6%, n = 83), which persisted at 25–48 hours (40.3%; n = 89; $p < 0.001$). However, there was no difference in the incidence of hypotension, tachycardia, or bradycardia at 5–24 hours (31.2%, 25.3%, and 4.5%, respectively) or at 25–48 hours (24.4%, 22.6%, and 3.2%, respectively). There was no indication that ketamine increased the risk for cardiac abnormalities (Supplemental Digital Content, **Table 9**, http://links.lww.com/CCX/A910).

Additional Adverse Effects

Adverse effects potentially associated with CI ketamine during the initial 7 days were evaluated in 381 patients and are described in **Table 3**. Increased secretions or suctioning were most commonly identified in 53 patients (13.9%), of which 39 (10.2%) were within the first 24 hours. Anticholinergic agents were initiated in 10 (2.6%) and mucolytics in two patients (0.5%). Emergence reactions at CI ketamine discontinuation were reported in 20 patients (5.1%). Additional dissociative effects were reported in 10 patients (2.6%) during the initial 7 days; however, the remaining adverse effects were less than 2%. Twenty-two patients (5.7%) required discontinuation of CI ketamine due to adverse effects with agitation, dissociative effects, or hemodynamic changes being the most common.

Pain

In the 24 hours prior to, the first 0–24 hours, and the 25–48 hours of CI ketamine, pain scores were recorded in 285 (85%), 293 (87%), and 178 (90%) patients a median of 10 (5–18), 11 (6–20), and 12 (6–20) times (p = 0.08), respectively. Goal pain scores were known in 50.1% of patients. There was a statistically significant increase in the proportion of time spent within goal pain score range after CI ketamine initiation (24 hr prior: 68.9% [66.7–72.6%], 0–24 hr: 78.6% [74.3–82.5%], 25–48 hr: 80.3% [74.6–84.3%]; $p < 0.001$) (**Fig. 2**, Supplemental Digital Content, http://links.lww.com/CCX/A910).

TABLE 3.
Adverse Effects During Continuous Infusion Ketamine Administration

AE, *n* (%)	First 24 hr (*n* = 381)	25–48 hr (*n* = 221)	Day 3 (*n* = 133)	Day 4 (*n* = 78)	Day 5 (*n* = 60)	Day 6 (*n* = 41)	Day 7 (*n* = 30)
Increased secretions or suctioning							
Yes	39 (10.4)	19 (8.6)	12 (9.0)	4 (5.1)	4 (6.7)	4 (9.8)	1 (3.3)
Medications started to control secretions[a]							
Atropine	1 (0.3)	–	–	–	–	–	–
Glycopyrrolate	2 (0.5)	1 (0.5)	–	–	1 (1.7)	–	–
Scopolamine	3 (0.8)	–	–	–	1 (1.7)	–	1 (3.3)
N-acetylcysteine	1 (0.3)	1 (0.5)	–	–	–	–	–
Seizure	1 (0.3)	–	–	–	–	–	–
Hypertonia	1 (0.3)	–	–	–	–	–	–
Allergic reaction	1 (0.3)	–	–	–	–	–	–
Injection site reaction	–	–	–	–	–	–	–
Additional AE reported							
Anxiety	–	–	2 (1.5)[b]	1 (1.3)	1 (1.7)	1 (2.4)	–
Agitation	5 (1.3)	–	1 (0.8)	2 (2.6)	–	–	1 (3.3)
Dissociative effects	6 (1.6)	1 (0.5)	2 (1.5) [b]	3 (3.8)	–	1 (2.4)	3 (10.0)
Self-extubation	1 (0.3)	–	–	–	–	–	–
Oversedation	1 (0.3)	–	–	–	–	–	–
Somnolence	2 (0.5)	–	–	–	–	–	–
Nystagmus	2 (0.5)	–	–	–	–	–	–
Vision changes	1 (0.3)	1 (0.5)	1 (0.8)	–	–	–	–
Itching	1 (0.3)	–	–	–	–	–	–
Wheezing	1 (0.3)	–	–	–	–	–	–
Ketamine discontinued due to an AE							
Yes	14 (3.7)	3 (1.4)	1 (0.8)	2 (2.3)	-	1 (2.4)	1 (3.3)

AE = adverse effect.
[a]Two were on anticholinergics at baseline and three had no documentation of increased secretions/suctioning.
[b]One patient experiencing anxiety and dissociative effects also used medical marijuana at the time these effects occurred.
Dashes indicate occurrence rate = 0%.

Sedation

In the 24 hours prior to, the first 0–24 hours, and the 25–48 hours of CI ketamine, sedation scores were recorded in 278 (80%), 304 (87%), and 182 (88%) patients a median of 7 (4–13), 8 (4–16), and 9 (5–14) times ($p = 0.045$), respectively. Goal sedation scores were known in 62.5% of patients. There was a statistically significant increase in the proportion of time spent within goal sedation score range after CI ketamine initiation (24 hr prior: 57.1% [52.5–60.0%], 0–24 hr: 64.1% [60.7–67.2%], 25–48 hr: 68.9% [65.5–79.5%]; $p < 0.001$) (Fig. 2, Supplemental Digital Content, http://links.lww.com/CCX/A910).

Analgesic, Sedative, and Antipsychotic Use

Analgesic and sedative requirements were found to be significantly reduced after the addition of CI ketamine. Median IV morphine equivalents decreased from 120 mg (25–400 mg) in the 24 hours prior to ketamine to 118 mg (10–363 mg) in the first 0–24 hours of the infusion and 80 mg (5–328 mg) in the 25–48 hours of the infusion ($p < 0.005$) (**Fig. 3**, Supplemental Digital Content, http://links.lww.com/CCX/A910). Median midazolam equivalents decreased from 11 mg (4–67 mg) in the 24 hours prior to ketamine to 6 mg (0–68 mg) in the first 0–24 hours of the infusion and 3 mg (0–57 mg) in the 25–48 hours of the infusion

(p < 0.001). Median propofol dose decreased from 942 mg (223–4,018 mg), to 160 mg (0–2,776 mg), and to 0 mg (0–1,859 mg) in the 24 hours prior to ketamine, the 0–24 hours of the infusion, and in the 25–48 hours of the infusion, respectively (p < 0.001). Median dexmedetomidine dose decreased from 1,025 μg (276–1,925 μg) in the 24 hours prior to ketamine to 285 μg (0–1,283 μg) in the first 0–24 hours of the infusion and 0 μg (0–826 μg) in the 25–48 hours of the infusion (p < 0.001) (**Fig. 4**, Supplemental Digital Content, http://links.lww.com/CCX/A910). Antipsychotic use was found in 44 of 351 patients (12.5%) at the time of ketamine initiation. This did not significantly change after the addition of CI ketamine as the proportion of patients on antipsychotics in the first 0–24, 25–48, and 49–72 hours was 12.4% (43/346), 12.7% (26/205), and 13.0% (16/123), respectively (p > 0.99). Antipsychotic use beyond 72 hours was not assessed as too few patients remained on ketamine.

Delirium

In patients able to be assessed for delirium, 110 (45%), 115 (46%), and 59 (41%) had a delirium screening performed in the 24 hours prior to, the first 0–24 hours, and 25–48 hours of CI ketamine, respectively. There was no difference in proportion of time spent positive for delirium after ketamine initiation (24 hr prior: 43.0% [17.0–47.0%], 0–24 hr: 39.5% [27.0–43.8%], 25–48 hr: 0% [0–43.7%]; p = 0.233) (**Fig. 5**, Supplemental Digital Content, http://links.lww.com/CCX/A910). Few patients remained on CI ketamine beyond 72 hours; therefore, proportion of patients positive for delirium could only be evaluated during this time frame. There was a total of 228, 266, 121, and 69 delirium screenings performed in the 24 hours prior to, the first 0–24, 25–48, and 49–72 hours of CI ketamine. The proportion of screenings positive for delirium was not significantly different across these time frames 45.2% (n = 103), 35.7% (n = 95), 40.5% (n = 49), and 37.7% (n = 26), respectively (p = 0.191). However, there was a significant reduction in the proportion of positive delirium screenings when comparing the 24 hours prior with the first 0–24 hours of CI ketamine (45.2% vs 35.7%; p = 0.041). This did not remain significant when the 24 hours prior to CI ketamine was compared with the other timeframes: 25–48 hours (45.2% vs 40.5%; p = 0.468), 49–72 hours (45.2% vs 37.7%; p = 0.336).

Patient Outcomes

Patient outcomes are consistent with a moderate to severely ill patient population with lengths of ICU and hospital stay on average greater than 1 and 2 weeks, respectively. The majority of patients survived and were discharged home (**Table 4**).

DISCUSSION

This large, multicenter study demonstrates widespread use of CI ketamine in many types of ICUs and highlights substantial variability in indication and dose but a clinically acceptable safety profile. After ketamine initiation, patients spent more time in goal pain and sedation score range with reduced exposure to other analgesics and sedatives, without increased delirium. These data are consistent with smaller studies evaluating ketamine as an analgesic and analgosedative agent in an ICU setting (4, 10, 16).

We identified practice variations in CI ketamine dose. Infusion dose units were not consistent but most were ordered in μg/kg/min and were titratable. However, many of these orders (24%) were not written with specific titration parameters, which is a safety concern not compliant with The Joint Commission on Accreditation of Healthcare Organizations

TABLE 4.
Clinical Outcomes Associated With Continuous Infusion Ketamine

Clinical Outcome	Value
Length of stay, d, median (IQR)	
ICU (n = 380)	9.9 (4.3–18.7)
Hospital (n = 381)	15.5 (7.4–27.5)
Duration of mechanical ventilation, d, median (IQR), n = 310	7.1 (2.9–15.7)
Mortality, n = 348, n (%)	
ICU	69 (19.8)
Hospital	73 (21.0)
Discharge disposition, n = 275, n (%)	
Home/correctional facility	149 (54.2)
Skilled nursing facility/long-term care/rehabilitation center	110 (40.0)
Transfer to another hospital	8 (2.9)
Hospice	8 (2.9)

IQR = interquartile range.

recommendations (17). Our data also suggest lack of ketamine weaning before discontinuation since median discontinuation doses were higher than starting doses. A high percentage of patients also remained on ketamine after extubation, which is plausible as ketamine does not impair respiratory drive at subanesthetic doses (1).

Ketamine is a sympathomimetic and negative inotrope known to inhibit catecholamine reuptake and monoamine transport and block L-type calcium channels (2, 3). Hypertension (5–25%) and tachycardia (2–62%) have been commonly reported in other trials (12). We found similar rates with hypertension occurring in 24% and tachycardia in 19.5% of patients. Hypertension was more common in the first 4 hours of the infusion compared with 5–24 and 48 hours. Hypotension has been reported in 16.3% of patients and cardiovascular collapse may occur in catecholamine-depleted patients (12, 18, 19). We found hypotension to be common, occurring in 23.5% of patients with a trend toward an increase in incidence during the 5–24 hours of the infusion. A high percentage of our patient population received vasopressors, but we found the hemodynamic effects remained the same regardless of vasopressor administration. Interestingly, median SBP, MAP, and HR in the 4 hours prior to ketamine use compared with the first 4 hours of the infusion remained unchanged. It also does not appear these hemodynamic changes increased the risk for cardiac abnormalities such as arrhythmias. The reasons for why we found such a wide variability in hemodynamic effects are unknown but possibly related to our study definitions, concomitant medication use, or confounding factors related to critical illness.

Common noncardiovascular adverse effects were secretions and need for anticholinergic or mucolytic medications (13.9% and 3.0%, respectively) and emergence reactions (5%). We found a 5.7% discontinuation rate due to adverse effects, mostly due to agitation/dissociative effects and hemodynamic changes that did not appear to relate to length of time on ketamine since most discontinuations occurred within the first 24 hours. This is similar to a rate of 7.7% reported in a previous study (20).

Pain and sedation were the most common indications for CI ketamine. Current consensus guidelines from the American Academy of Pain Medicine endorse ketamine use for the treatment of acute pain in certain patient populations, however, specific recommendations on its use as a CI in the ICU are lacking (21). Ketamine has been shown to reduce opioid requirements in both trauma and surgical ICU patients (4, 10). A recent meta-analysis evaluating adjunctive analgesic use in the critically ill found ketamine use was associated with reduced opioid requirements by a mean difference of 36.81 mg (95% CI, 27.32–46.30 mg) of oral morphine equivalents in 24 hours (22). Within 48 hours of ketamine initiation, we were able to show a median difference of 120 mg oral (40 mg IV) morphine equivalents, as well as improved time in goal pain score range. Reducing opioid requirements during ICU stay may have significant downstream effects as 12–73% of ICU survivors report chronic pain with a similar proportion being prescribed opioids at discharge (23–25). Additionally, it has been shown that 4–19% will become chronic opioid users irrespective of opioid use prior to admission (23–25). It is unknown if high doses or prolonged infusions of opioids in the ICU are associated with chronic opioid use but those receiving opioids during a hospitalization are twice as likely to have opioids prescribed at discharge than those not receiving opioids (26). In addition to transitioning to chronic use, other risks of opioids include nausea and vomiting, constipation, ileus, immunosuppression, and delirium. Therefore, use of nonopioid pain medications, such as ketamine, that can reduce opioid exposure, may reduce these risks.

Ketamine has been evaluated as an analgosedative agent in the ICU and its reported effects on sedation practices are variable. Several small, retrospective, observational studies have demonstrated that ketamine may reduce exposure to opioids and sedatives (4, 16, 20, 27–29) and improve time spent in goal sedation score range (20, 29). A recent meta-analysis included 15 studies (12 observational, three randomized) evaluating the use of CI ketamine for sedation in 892 mechanically ventilated patients (12). Doses and dose strategies (fixed dose vs titration) were inconsistent and ranged from 0.05 to 4.9 mg/kg/hr. Ketamine use was associated with reduced infusion rates of propofol (mean difference, –699 μg/min [95% CI, –1,168 to –230 μg/min]; $p = 0.003$) but failed to demonstrate any effect on fentanyl (mean difference, –21.5 μg/hr [95% CI, –48.2 to 5.1 μg/hr]; $p = 0.11$) or midazolam (mean difference, –0.3 mg/hr [95% CI, –0.95 to 0.35 mg/hr]; $p = 0.37$) requirements. Ketamine did not improve the ability to achieve goal sedation (odds ratio, 0.51; 95% CI, 0.14–1.88; $p = 0.31$). However, they looked at the number of measurements at goal sedation that may be dependent upon the frequency or timing of assessments made, or the number of patients at goal sedation that may be a static measure at a single moment in time, rather than evaluating the effects over time. In contrast, our study found improvements in target sedation according to proportion of time spent in goal sedation score range measured throughout the treatment period. This is a more clinically meaningful endpoint as it captures the magnitude of effect over a prolonged time frame compared with a single point in time.

The impact of ketamine on ICU delirium is unknown. It may potentially mitigate or prevent delirium by reducing neuroexcitation and inflammatory cytokines or by reducing exposure to known deliriogenic medications. However, it may also increase the risk for delirium due to its known psychotomimetic effects (30–34). There are mixed findings related to ketamine and delirium in the literature. One study demonstrated CI ketamine can decrease the duration of delirium independent of reducing exposure to opioid and sedative infusions and another found no difference in number of days alive without delirium or coma, although ketamine treated patients had a higher percentage with coma, which likely confounded detection of delirium (30, 31). These data, despite limitations, indicate ketamine does not appear to increase the risk for delirium, which is similar to our findings. It also highlights the low frequency at which delirium is assessed, which was also demonstrated in our study. On the other hand, a more recent analysis by Wu et al (34) did find an association between ketamine use and ICU delirium using a more rigorous multivariable, time-dependent model in 925 critically ill patients. The median dose of ketamine used was 0.5 mg/kg/hr, which is higher than average doses seen in other studies including this report. Further data are needed to explore the dose response effect of ketamine on ICU delirium.

Our study is novel by evaluating ketamine use across multiple geographically diverse institutions. We included a large sample size of patients, evaluated endpoints relevant to clinical practice, and had clear definitions to limit variability in data collection. There are several limitations mainly due to the retrospective design with lack of a comparison group and potential missing or incomplete data. The study period was from 2014 to 2017 and the majority of patients included were from five of the 25 participating institutions. Usage patterns may have changed since this time frame and the results are only representative of a sample of institutions across the country. Additionally, not all patients who received ketamine during this time frame were included. We did include the most recent patients receiving ketamine, but there is still the potential for selection bias. Having multiple data collectors may have raised inconsistencies in data collection. However, we attempted to ensure data integrity prior to study initiation by having a standardized data collection tool, data dictionary, extensive testing and refinement by the study group and participating site investigators, and conference calls to field questions and provide consensus on how certain data points should be collected. As many confounders are likely present in critically ill patients, the hemodynamic effects seen with CI ketamine can only be used to describe the patient population receiving this therapy. The rationale for adding ketamine to current pain and sedation regimens were not consistently documented; therefore, we can only assume that it was due to failure to achieve goal pain and sedation scores in those already receiving conventional therapy. The goal levels of pain and sedation were not known in a large percentage of patients likely due to poor chart documentation. Therefore, we had to make assumptions that could limit generalizability. Not all patients received analgesia; therefore, our results might not apply to patients receiving an adequate multimodal approach to pain. We found very few patients with documented delirium screenings and it is also unknown if the ICU liberation (A to F) bundle, an intervention known to reduce the duration of delirium, was used in these patients. Therefore, any associations on the risk of delirium with CI ketamine cannot be concluded from these data. Since we did not have a comparator group, it is also possible that time played a role in reducing doses of analgesics and sedatives as patients may have been improving clinically. Regardless, proportion of time spent in goal pain/sedation score range improved after the addition of CI ketamine. Including a group of diverse institutions adds strength, but it also limits the applicability due to heterogeneity in pain and sedation practices. We did not perform an economic analysis or compare ketamine to other sedatives on time spent in the ICU or on the ventilator, however, ketamine is relatively inexpensive compared with other agents. Despite these limitations, this study adds to the body of literature demonstrating the benefits of CI ketamine and clinicians could consider this therapy to reduce exposure to opioids and improve proportion of time in goal pain/sedation score range for critically ill patients.

CONCLUSIONS

In the largest study to date exploring the effects of real-world CI ketamine use in the ICU, a greater proportion of time was spent in goal pain and sedation score range with a reduction in exposure to other sedatives and analgesics in the short time frame after it's initiation. This is in addition to an acceptable safety profile and no observed increase in time spent positive for delirium. Ketamine can be considered in critically ill patients, especially in those failing traditional analgesic and sedative agents. It can be used to decrease exposure to opioids and known deliriogenic sedatives such as benzodiazepines, but larger, randomized controlled trials for its proposed indications are necessary to guide appropriate use and determine its economic value in reducing time in the ICU and on the ventilator.

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