Continuous Intravenous Ketamine for Sedation in the Intensive Care Unit

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Abstract

Background: Current literature regarding the use of ketamine for sedation and other non-analgesic indications is limited and variable. Further research is needed to identify an optimal dosing strategy for these indications.

Objective: The primary objectives are to describe the use of continuous intravenous (IV) ketamine for sedation and to determine an appropriate initial dosing rate.

Methods: Continuous IV ketamine infusions between 3/1/2014 and 7/31/2017 were screened for indication. Various dosing parameters were collected by chart review for the sedation indication. A subset of these infusions were included in an initial dosing analysis that compared initial infusion rates of less than 0.5 mg/kg/hr to higher rates. The primary endpoint was the rate of goal Richmond Agitation-Sedation Scale (RASS) achievement 8 hours after the infusion began.

Results: The initial dosing analysis included 33 infusions. In the low dose group, 6 of 16 infusions (37.5%) attained goal RASS at 8 hours compared to 11 of 17 (64.7%) in the high dose group (p=0.17). At 8 hours, 7 (43.8%) of the patients receiving low dose infusions were agitated compared to 4 (23.5%) of the high dose infusions (p=0.28). Both groups had a similar rate of oversedation at 8 hours and a similar maximum infusion rate.

Conclusions: Higher initial ketamine doses were not significantly associated with target RASS attainment at 8 hours. However, there was a trend towards more agitation at 8 hours in the low dose group and rates of oversedation were similar between the two arms.

Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist which causes a blockade of excitatory synaptic activity and a loss of responsiveness.[1] This unique mechanism of action supports its use for a variety of indications, including maintenance and procedural sedation, adjunct analgesia, and rapid sequence intubation. Notable advantages of ketamine over common sedatives such as propofol and midazolam include improved hemodynamic stability and preservation of respiratory drive. Ketamine also has anticholinergic and glutamatergic properties that contribute to its utility in bronchospasm and refractory status epilepticus (RSE), respectively.[2]

Ketamine has several prominent side effects that should be considered before its use. Patients may experience an out of body experience known as an "emergence reaction" with associated agitation and hallucinations.[2] This reaction frequently occurs at sub-anesthetic doses during the induction or weaning phases of an infusion. Benzodiazepines are commonly used to counteract emergence reactions during ketamine de-escalation; however, recent reviews report success with antipsychotic agents as well.[3] Other side effects are attributed to increased sympathetic response, such as hypertension and tachycardia. Antihypertensive agents can be given as needed to limit the hemodynamic effects.

The data to support the use of continuous intravenous (IV) ketamine for intensive care unit (ICU)-specific indications, such as sedation, is limited and dosing recommendations vary widely.[4] There is a lack of prospective randomized trials to evaluate the efficacy of different regimens and most retrospective reviews include heterogeneous patient populations. One review outlined 20 different case studies and case reports of ketamine for maintenance sedation.[4] Different dosing regimens were used in every included report and 3 different dosing units were utilized. Further analysis is required to define the optimum dosing range.

Due to the lack of evidence to support specific dosing strategies, the primary objectives of this study were to describe the use of continuous IV ketamine for sedation within a large hospital system and to determine an appropriate initial dosing rate. Our hypothesis was that higher initial doses of ketamine would lead to a higher rate of goal sedation attainment shortly after infusion initiation.

Methods

We conducted a retrospective review of all adult patients who were treated with a standard concentration ketamine infusion (500 mg/250 mL) at any Aurora Health Care (AHC) hospital. We identified patients through pharmacy medication administration records from March 2014 to July 2017. Aurora's Institutional Review Board (IRB) determined the intent of this project did not constitute human subject research and as such, did not require Aurora IRB oversight. Patients were excluded if the infusion was ordered from an adjunct analgesia order-set or if ketamine was used for a non-sedation indication determined via manual review of the electronic health record.

The remaining subset of patients were further screened for demographics, ketamine dosing and duration. Richmond Agitation-Sedation Scale (RASS) scores were also collected for all included patients. RASS is a clinically validated tool used to measure the agitation or sedation level of a patient.[5] The scale ranges from +4, indicating combativeness, to -5 which describes an unarousable patient. Any RASS goal specified in the ketamine order was utilized as that particular infusion's goal. However, if no such range was specified, the default goal was 0 to -2, indicating light sedation.

Patients that had a ketamine infusion for sedation continued for more than 8 hours were included in an initial dosing analysis. Nurses commonly have standing orders to chart a RASS score every 4 hours, therefore, the 8 hour timeframe was chosen to allow for interpretation of at least 2 RASS scores. Patients were excluded from this analysis if they did not have any RASS documented during the infusion or if they were being treated with comfort measures only. Any patient treated with a concomitant neuromuscular blocker was also excluded to allow for appropriate interpretation of RASS scores. Patients with an infusion initiated at < 0.5 mg/kg/hr (low dose group) were compared to patients with an infusion initiated at > 0.5 mg/kg/hr (high dose group). The decision to use 0.5 mg/kg/hr as the cutoff was based on preliminary data of the average initial dosing rates from our institution. At AHC, ketamine dosing is calculated based on the patient's actual body weight.

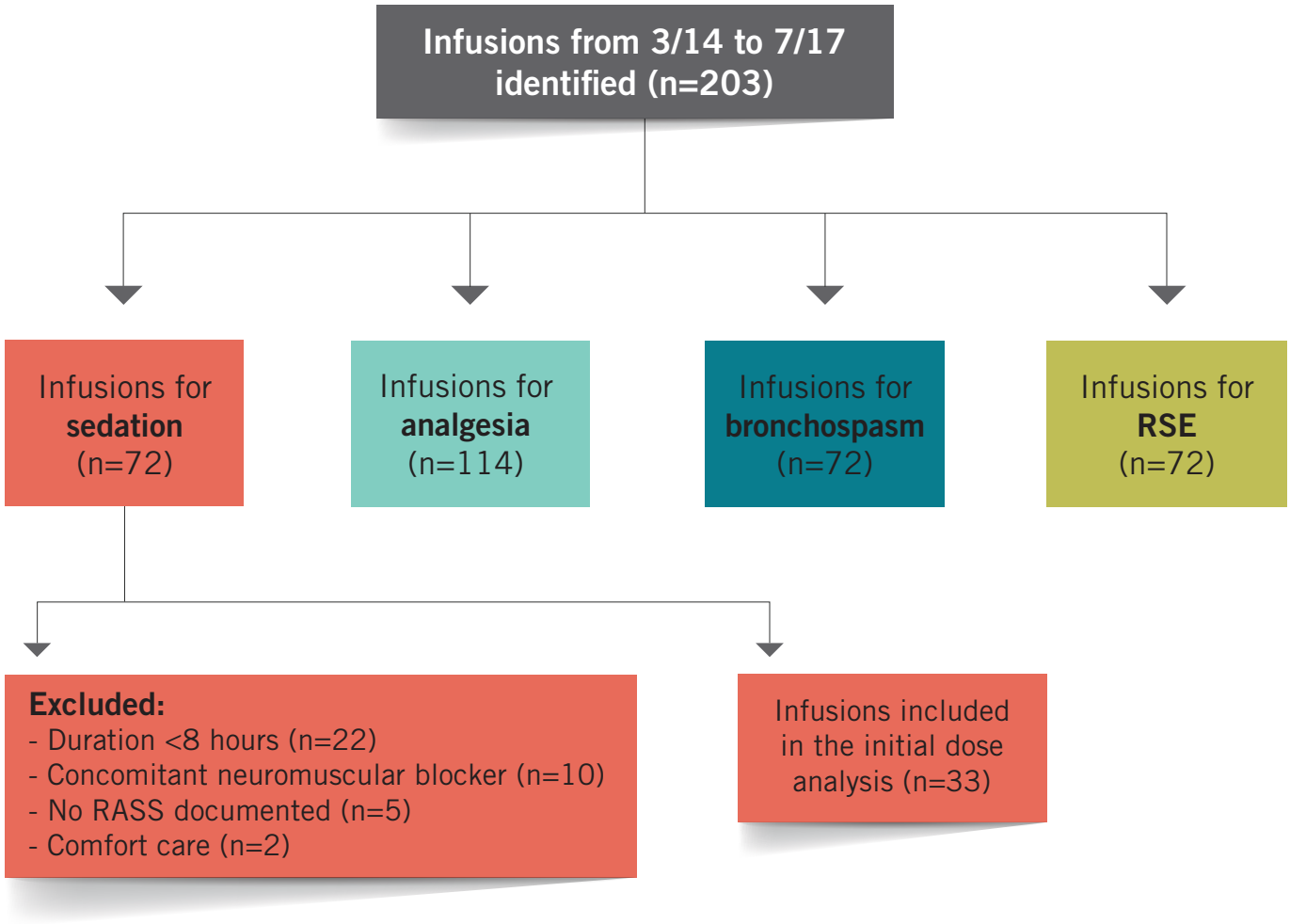
The primary outcome was the rate of

TABLE 1. Demographics and Dosing Regimens for Included Sedative Infusions

Number of Infusions	33
Age, years (median, IQR)	59 (47-66)
Male Gender	16 (58.5%)
Weight, kg (median, IQR)	84 (68-105)
Intubated	29 (87.9%)
Duration, days (median, IQR)	1.45 (0.93-1.96)
Number of Bolus Doses Given	12 (36.4%)
Bolus Dose, mg/kg (median, IQR)	1.46 (0.93-2.20)
Initial Rate, mg/kg/hr (median, IQR)	0.5 (0.2-0.5)
Maximum Rate, mg/kg/hr (median, IQR)	1 (0.5-1.2)

IQR, interquartile range

FIGURE 1. Ketamine Infusion Inclusion Flow-Chart



goal RASS attainment at hour 8 of the infusion. Secondary outcomes included the maximum infusion rate, the rate of agitation at hour 8, the rate of oversedation at hour 8, the percentage of time within the goal RASS range and adverse reactions.

Statistical Analysis

Continuous variables are reported as median and interquartile range (IQR). Dichotomous variables were compared using Fisher's exact test, when appropriate. We considered p values of < 0.05 to be statistically significant. Microsoft Excel 2010 (Redmond, WA) was used for data collection and statistical analysis.

Results

Continuous IV infusion ketamine was administered to 203 patients from March 2014 to July 2017 (Figure 1). There were 114 infusions used primarily for analgesia, 72 for sedation, 14 for bronchospasm, and 3 for RSE. The subset of interest included 33 infusions for sedation. Patient demographics and characteristics of the ketamine regimens are described in Table 1. Over half of the patients were male with a median age of 59 (IQR 47-66) years. Twelve (36.4%) patients received a bolus dose prior to the infusion. The median initial infusion rate was 0.5 (IQR 0.2-0.5) mg/kg/hr with a range of 0.02-1 mg/kg/hr. The median maximum infusion rate was 1 (IQR 0.5-1.2) mg/kg/hr with a range of 0.2-3.5 mg/kg/hr. Ketamine was continued for a median duration of 1.45 (IQR 0.93-1.96) days. The majority of ketamine infusions were being titrated to the standard RASS goal of 0 to -2. However, 4 patients in each group had more aggressive sedation goals (i.e. RASS -1 to -3 or -3 to -4).

The initial dosing analysis included 33 patients (Table 2). There were 16 patients in the low dose group started on a median initial rate of 0.2 (IQR 0.18-0.2) mg/kg/hr. The 17 patients in the high dose group were started on a median initial rate of 0.5 (IQR 0.5-1) mg/kg/hr. Median maximum infusion rates were similar at 0.95 (IQR 0.5-1.05) and 1 (IQR 0.5-1.3) mg/kg/hr for the low dose and the high dose groups, respectively. In the low dose group, 6 (37.5%) patients achieved goal RASS at hour 8 compared to 11 (64.7%) patients in the high dose group (p=0.17). Conversely, 7 (43.8%) patients were agitated at hour 8 in the low dose group compared to 4 (23.5%) in the high dose group (p=0.28). The rate of oversedation at hour 8 and percentage of time at goal RASS was comparable between the two arms.

Ketamine's use in this subset of patients lead to 4 (25%) adverse reactions in the low dose group compared to 2 (11.8%) in the high dose group (p=0.4). Emergence reactions were the most common side effect; however, there was one case of

atrial fibrillation and one patient with volume overload attributed to the ketamine infusion. Volume overload occurred after a ketamine infusion reached a maximum rate of 3.5 mg/kg/hr (147 mL/hr in an 84 kg patient). Providers used various strategies to prevent emergence reactions, and they were similar between both low and high dose groups. Common prophylactic interventions included continuous infusions of other sedatives, intermittent doses of benzodiazepines or intermittent antipsychotics. The use of concomitant IV analgesics and sedatives were also heterogeneous, but rate changes in the first 8 hours did not differ greatly between the two groups (Table 2). In both treatment arms combined, there were 17 (51.2%) patients that had concomitant vasopressors when ketamine was initiated. Four hours after initiation, 11 (64.7%) of the vasopressor infusion rates had decreased from baseline.

Discussion

To our knowledge, this is the first study comparing the efficacy of different initial IV ketamine dosing rates for sedation in critically ill patients. We report a trend towards increased rate of target sedation attainment with initial rates > 0.5 mg/kg/hr compared to lower doses. This trend was not reproduced in the comparison of overall time in goal RASS range. However, in theory, similar time at goal may be more related to increased agitation while weaning off the infusion rather than the initial infusion rates. Maximum infusion rates were similar in both groups, indicating nurses and providers felt the level of sedation was inadequate at lower infusion rates. This finding also explains the similar rate of emergence reactions between groups.

In our population of patients receiving ketamine for sedation, the median starting rate was 0.5 mg/kg/hr and the maximum rate was 1 mg/kg/hr. Groetzinger et al reported successful adjunct sedation using lower infusion rates than the present study.[3] The median starting rate was only 0.1 mg/kg/hr with a median maximum rate of 0.6 mg/kg/hr. However, included patients were required to have an additional continuous sedative infusing with light sedation goals. In contrast, Umanna et al utilized ketamine

TABLE 2. Initial Dose Comparison

	< 0.5 mg/kg/hr (n=16)	*≥ 0.5 mg/kg/hr (n=17)*
Number of Bolus Doses	6 (37.5%)	6 (35.3%)
Bolus Dose, mg/kg (median, IQR)	1.92 (1.25-2.08)	0.96 (0.89-2.05)
Initial Rate, mg/kg/hr (median, IQR)	0.2 (0.18-0.2)	0.5 (0.5-1)
Maximum Rate, mg/kg/hr (median, IQR)	0.95 (0.5-1.05)	1 (0.5-1.3)
Intubated	16 (100%)	13 (76.5%)
8 Hour RASS		
At Goal[a]	6 (37.5%)	11 (64.7%)
Oversedated	3 (18.8%)	2 (11.8%)
Agitated[b]	7 (43.8%)	4 (23.5%)
Percentage of Time		
At Goal[c]	54.2%	56.9%
Oversedated	29.7%	25.0%
Agitated	16.1%	15.6%
Adverse Reactions		
All	4 (25%)	2 (11.8%)
Emergence Reaction	2 (12.5%)	2 (11.8%)
Volume Overload	1 (6.3%)	0
Atrial Fibrillation	1 (6.3%)	0
Strategy to Avoid Emergence		
None	3 (18.8%)	4 (23.5%)
Continuous Sedative	9 (56.3%)	9 (52.9%)
Intermittent Benzodiazepine	6 (37.5%)	4 (23.5%)
Intermittent Antipsychotic	3 (18.8%)	4 (23.5%)
Concomitant Medications[d]		
Fentanyl	11 (68.8%)	7 (41.2%)
Fentanyl Change, mcg/hr (median, IQR)[e]	-15 (-37.5-0)	0 (-12.5-7.5)
Midazolam	4 (25%)	3 (17.7%)
Midazolam Change, mg/hr (median, IQR)[e]	1 (-1.75-2.75)	0 (-3-0)
Propofol	8 (50%)	8 (47.1%)
Propofol Change, mcg/kg/min (median, IQR)[e]	-5 (-25-12.5)	0 (0-3.38)
Dexmedetomidine	5 (31.3%)	3 (17.7%)
Dexmedetomidine Change, mcg/kg/hr (median, IQR)[e]	0 (-0.1-0.3)	-0.6 (-0.9-0.3)
Fentanyl + Other Sedative	2 (12.5%)	1 (5.9%)
No Other Sedative	3 (18.8%)	5 (29.4%)

RASS, Richmond Agitation-Sedation Scale; IQR, interquartile range
[a]p=0.17
[b]p=0.28
[c]Percentage of time at goal describes the number of RASS data points that met their particular goal range throughout the entire duration of the ketamine infusion
[d]Medications that had been infusing for any amount of time within the first 8 hours of the ketamine infusion
[e]Rate change that occurred from ketamine infusion initiation to hour 8

for sedation at an average rate of 2 mg/kg/hr.[6] However, these reviews did not compare different dosing strategies and we are unable to draw conclusions based on their dosing parameters alone.

Due to infrequent use, we were unable to effectively evaluate dosing strategies for the bronchospasm or RSE indications. The dosing rate for bronchospasm has previously been reported to range from 0.15 to 2.5 mg/kg/hr, but the optimal regimen has not been established.[7] There is some data to support higher doses for RSE. Gaspard et al reported ketamine was a relatively effective and safe drug for RSE, but treatment was never successful when the infusion rate was < 0.9 mg/kg/hr.[8] Similarly, Synowiec et al reported 100% effectiveness in 11 patients that received a mean dose of 1.3 mg/kg/hr.[9]

Limitations

There are several important limitations to the present study. This was a retrospective study and it is difficult to attribute any patient-level trends to ketamine doses without a randomized controlled trial. Ketamine's relatively infrequent use at AHC contributed to a low sample size. As such, this trial may not have been powered to find statistically significant differences in RASS scores or other outcomes.

The population described in this study is relatable to many critically ill patients being treated in an ICU; however, this led to a very heterogeneous population with various disease states, severity of illnesses and concomitant medications. We were unable to control for many factors that could have affected outcomes, such as pain, medication withdrawal, ventilator settings, procedures, as needed medications and others. RASS goals were not standardized for the entire population, thus dosing rates may have been decreased had we only included patients with light sedation goals. In addition, we were unable to accurately characterize the ketamine infusion outside of predetermined dosing data points. Information relating to adverse reactions was gathered from physician progress notes, and some side effects may have been missed if they were not adequately documented. On the other hand, it is difficult to prove causality of the reported emergence reactions, atrial fibrillation and volume overload. For example, inadequate sedation or ICU-related delirium can mimic the agitation seen with emergence reactions.

The RASS scoring system has previously been validated in heterogeneous patient populations.[5,10] However, prospective validation has not occurred in patients receiving ketamine and it is unclear if RASS scores are as reliable in this population. Ketamine's unique mechanism leads to dissociative sedation during which patients may spontaneously move or open their eyes. As such, RASS may not be ideal, but alternative scoring systems to address this scenarioare lacking.

RASS documentation was generally reliable; however, inadequate documentation led to the exclusion of 5 patients from the initial dosing analysis. In some cases, RASS scores were not charted in a timely manner or ketamine rate titration was not consistent with the temporal RASS score. Unlike other sedatives such as propofol and midazolam, ketamine does not currently have an order-set with appropriate monitoring for ICU-specific indications at AHC. An order-set is currently being developed to improve monitoring, limit dosing variability and prevent emergence reactions while utilizing ketamine for ICU-specific indications.

Conclusion

Higher initial ketamine rates were associated with nonsignificant trends towards higher target RASS attainment and less agitation at 8 hours after infusion initiation. Regardless of initial dosing rate, patients received similar maximum dosing rates. The findings suggest that patients may achieve adequate sedation faster with an initial dosing rate of > 0.5 mg/kg/hr, but this should be confirmed in an adequately powered randomized controlled trial. Despite the heterogeneous patient population and small sample size, we believe this study contributes to the limited literature describing the use of continuous IV ketamine for sedation in critically ill patients.

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