Original Research

Effect of Ketamine on Vasopressor Needs in Mechanically Ventilated Patients: A Retrospective Study

Channing Hui, DO[1], Joao Filipe Monteiro, Ph.D[2], Dyuti Trivedi, MS[3], Dhruv Vasant, MD[2], Gerardo Carino, MD, Ph.D[1]

[1] Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Warren Alpert Medical School of Brown University,

[2] Medicine, Warren Alpert Medical School of Brown University,

[3] Center for Behavioral and Preventive Medicine, The Miriam Hospital, Providence, Rhode Island, USA

Article Information

Abstract

Background

Ketamine has many recognized effects that may be beneficial in patients undergoing mechanical ventilation. While ketamine provides sedation and analgesia, it has additional sympathomimetic properties that may help support critically ill patients in shock. We hypothesized patients undergoing mechanical ventilation with continuous ketamine infusion as an adjunct to sedation agents would be associated with a lower vasopressor requirement.

Methods

We performed a retrospective cohort study on 200 mechanically-ventilated patients (205 hospital encounters) in two academic hospitals between 2015 to 2019. Patients on ketamine as an adjunct (K-G) to another sedative were utilized as the intervention group. Patients on both propofol and fentanyl (PF-G), a common sedation regimen, were used as the control group. The primary outcome was vasopressor requirements before and after initiation of ketamine or propofol and fentanyl. Secondary outcomes included all-cause mortality, 30-day mortality, ICU length-of-stay (LOS), hospital LOS, and ventilator-free days.

Results

The overall proportion of males was 63.4% (p-value =0.5016). The norepinephrine average dose (up to 48 hours after initiating sedatives) was lower in K-G (8.7 mcg/kg/min) when compared with PF-G (14.2 mcg/kg/min), p-value<0.0001. The ICU, 30-day or any time all-cause mortality was similar in both groups (22.0, 21.5 and 32.2%, p-value=0.8952, 0.9709, 0.8019, respectively). The average ICU and hospital stay overall were 8.8 (p-value=0.5174) and 16.6 (p-value=0.9280) days, respectively. The average ventilator-free days for K-G was 22.8 days compared to 23.2 days in PF-G (p-value=0.5567).

Conclusions

In our study, ketamine as an adjunct sedation agent was associated with decreased vasopressor requirements in patients on mechanical ventilation when compared to the standard use of propofol and fentanyl. Further prospective research is necessary before ketamine can be broadly recommended as an adjunct to sedation in critically ill patients with shock.

BACKGROUND

Ketamine has been available for more than fifty years and has been traditionally utilized more commonly in the pediatric population.[1-3] It is a frequently used medication in the emergency department for procedural sedation. Ketamine is accepted as a useful alternative to opiates at sub-dissociative doses for analgesia.[4] Its use has grown in the adult population for post-operative pain management and refractory depression.[5-7]

In recent years, ketamine has been gaining attention as a choice for continuous sedation in patients on mechanical ventilation as it possesses both sedative and analgesic properties and minimal effect on respiratory drive.[8] The known adverse effects of the more common sedation agents such as propofol, dexmedetomidine, benzodi-

azepines, and opiates make alternative agents desirable. Both propofol and dexmedetomidine have well-known adverse side effects of hypotension and can be a cause of initiating vasopressor use.[9,10] Dexmedetomidine has a higher incidence of both hypotension and bradycardia when compared to midazolam as sedation for prolonged mechanical ventilation.[11] Although unclear whether vasopressors are the direct cause of increased mortality or the disease severity requiring vasopressor use, increased vasopressor requirements have been associated with increased mortality.[12-14]

Ketamine provides a sympathomimetic response that may be beneficial to patients in shock. In a study of 130 volunteer patients, the results suggested that ketamine may increase the blood pressure during the initial use of continuous infusion, mimicking a vasopressor response.[15] Similar results were observed in a smaller study of 20 subjects.[1] Other studies in ventilated patients have suggested lower vasopressor needs in patients sedated with ketamine. In a retrospective study examining ventilated patients with continuous infusion of ketamine as an adjunct, 70.5% of patients had a decrease or no vasopressor requirement after 24 hours, once ketamine was initiated.[16] Another retrospective study showed a decreased vasopressor requirement at 6 hours post-ketamine, but no difference at 24 hours.[17] In a study of patients with septic shock, ketamine was associated with a trend to lower vasopressor need and a reduction in other sedation needed.[18] Our study seeks to examine the vasopressor response for a more prolonged period of 48 hours after initiation of ketamine.

Since ketamine is often an adjunct to another sedation agent, we hypothesized that mechanically ventilated patients sedated with a continuous ketamine infusion as a second agent will have a lower vasopressor requirement compared to patients sedated with two alternate drugs. In our study, we chose to compare patients on both propofol and fentanyl infusions (PF-G) to this ketamine group (K-G).

METHODS

We performed a retrospective cohort study on adult patients admitted to intensive care units (ICU) in two large academic hospitals in Rhode Island between April 2015 and September 2019. Inclusion criteria were patients greater than 18 years of age undergoing mechanical ventilation. The intervention group included patients on continuous ketamine as an adjunct to another sedative. The control group included patients on simultaneous propofol and fentanyl continuous infusions. We allowed for the same patients to be part of the study if they were readmitted and satisfied the inclusion criteria for the same study group. We excluded patients who were readmitted and met criteria for both study groups during the time-

frame. We screened a total of 3322 hospital encounters (2972 patients) between April 2015 and September 2019. Those who satisfied the inclusion criteria for both study groups, 410 hospital encounters (372 patients) were examined further. There were 40 hospital encounters (25 patients) that were readmitted and met criteria for both study groups during the timeframe; these encounters were excluded. Of the 370 hospital encounters (347 patients), we randomly selected 291 hospital encounters (274 patients) for analysis. Of 291 hospital encounters, 86 hospital encounters (82 patients) were excluded because these patients did not satisfy inclusion criteria upon chart review (Figure 1). Our study was approved by the Institutional Review Board (1373059-1) and informed consent was waived.

Baseline characteristics obtained were age, gender, weight (kilograms), race (White/Caucasian, Black/African American, others), and primary diagnoses. Height and weight were collected to calculate body mass index (BMI).[19] Glasgow coma scale (GCS) assessed for consciousness.[20] The Confusion assessment method for intensive care unit (CAM-ICU) score assessed for delirium on arrival to the ICU, as well as before and after sedation.[21] The Acute Physiology and Chronic Health Evaluation II (APACHE II score) and Charlson Comorbidity index (CCI) were measured to predict risk of mortality.[22,23]

Outcome measures

The primary outcome was defined as the dose of norepinephrine up to 12 hours before and 48 hours after the initiation of either ketamine for the intervention group, or the initiation of both propofol and fentanyl for the control group. We defined this initiation point as time 0 hour. The hourly doses of norepinephrine within this timeframe were recorded. An analysis was performed to calculate the average doses in 12-hour blocks, up to 12 hours before and 48 hours after time 0 hour. Blood pressure targets were not protocolized, however a minimum mean arterial pressure (MAP) of 65 mmHg was most often clinically targeted.

Our secondary outcomes include mortality, ICU length-of-stay (LOS), hospital LOS, ventilator-free days within 28 days, and overall concomitant sedative continuous infusions including dexmedetomidine, propofol, fentanyl, and midazolam. Mortality rates were categorized to all-cause, 30-day, ICU, and in-hospital. All-cause mortality was defined as death from any cause up to 6 months after discharge. Proportion of patients on other sedatives, such as dexmedetomidine and midazolam, was calculated within K-G and PF-G groups. Ventilator-free days were defined based on days off the ventilator within 28 days. Patients on the ventilator for more than 28 days were considered to have 0 ventilator-free days.
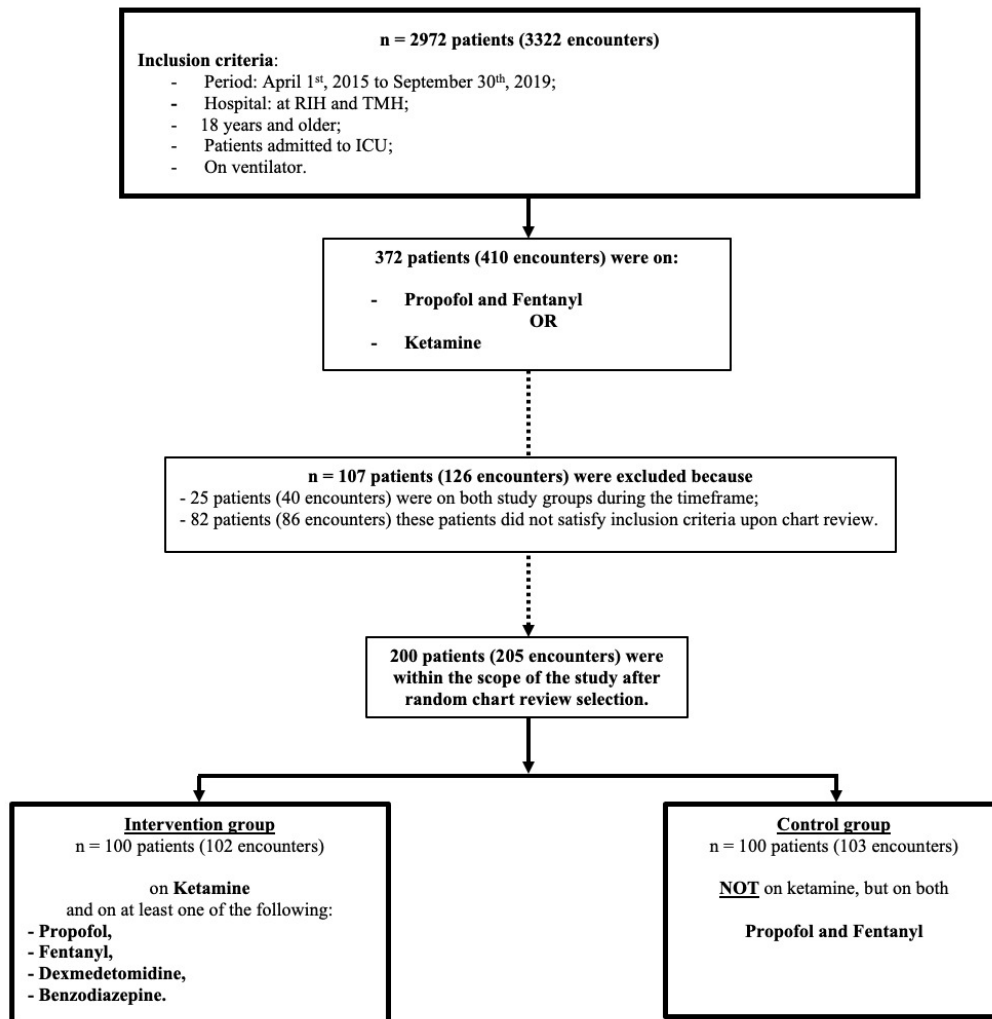
Figure 1. Flow chart identifying patients in the two study groups.

Abbreviations: ICU – Intensive Care Unit; RIH – Rhode Island Hospital; TMH – The Miriam Hospital.

Statistical Analysis

Study data were collected and managed using REDCap electronic data capture tools.[24,25] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies,

The analysis was conducted in SAS© software (Version 9.4, SAS Institute Inc., Cary, NC), where chi-square and Student's t-tests were performed for descriptive analyses to report and compare the study groups on demographics, norepinephrine dose (12 hours before, and up to 48 hours after time 0), average norepinephrine dose usage by hour, mortality, concomitant sedative medications, LOS, and ventilator-free days.[26]

RESULTS

The final analytical sample had 205 hospital encounters (200 patients), 102 (49.8%) hospital encounters (100 pa-

tients) in the intervention group, 103 (50.2%) hospital encounters (100 patients) in the control group.

The intervention group had fewer Black/African American patients (6.3%) compared to the control group (19.6%) (p-value= 0.0155). The average age for the intervention group was 48.6 years (with standard deviation (SD)=16.1) and the control group was 48.5 years (SD=15.5) (p-value=0.9910). The average APACHE II score (16.9 and SD=7.1) and CCI (1.0 and SD=1.3) were comparable between the two groups (p-value=0.9853 and 0.2057, respectively). The weight and the BMI were similar between the two study groups, with the averages of 83.1 kg (SD=27.5) and 29.2 kg/m^2 (SD=9.5) (p-value= 0.1024 and 0.2744, respectively). The proportion of patients with positive CAM-ICU on arrival to ICU was similar in the two study groups, with an overall proportion of 90.5 (p-value=0.8629) (Table 1). For the primary diagnosis of trauma or surgery, ketamine was not utilized in any patients in the K-G (p-values= <0.0001 and 0.0016, respectively). For patients with the primary diag-

Table 1. Baseline characteristic on ICU admission.

Patient characteristics	Study group		Overall (n=205)	P-value
	Intervention group 49.8% (n=102)	Control group 50.2% (n=103)		
Male gender, no. (%)	67 (65.7)	63 (61.2)	130 (63.4%)	0.5016
Race*, no. (%)				0.0155
White or Caucasian	74 (77.9)	72 (70.6)	146 (74.1)	
Black/African American	6 (6.3)	20 (19.6)	26 (13.2)	
Other/unknown/Refuse to answer	15 (15.8)	10 (9.8)	25 (12.7)	
Hispanic, no. (%)	16 (19.3)	10 (9.9)	26 (14.1)	0.0692
Age, Mean (SD)	48.6 (16.1)	48.5 (15.5)	48.5 (15.7)	0.9910
Weight (kg), Mean (SD)	86.5 (28.6)	80.0 (26.3)	83.1 (27.5)	0.1024
BMI, Mean (SD)	30.0 (9.5)	28.5 (9.4)	29.2 (9.5)	0.2744
Abnormal blood pressure[a]	0 (0.0)	2 (1.9)	2 (1.0)	0.4981
GCS, Mean (SD)	6.3 (5.4)	5.8 (5.1)	6.1 (5.2)	0.4642
Positive CAM-ICU score[b], no. (%)	92 (90.2)	90 (90.9)	182 (90.5)	0.8629
Delirious before sedation[c,]	39 (55.7)	48 (54.6)	87 (55.1)	0.8834
Delirious after sedation[c]	87 (85.3)	76 (76.8)	163 (81.1)	0.1227
Reason for ICU admission				
Respiratory failure	29 (28.4)	24 (23.3)	53 (25.8)	0.4016
Trauma	0 (0.0)	20 (19.4)	20 (9.8)	<0.0001
Surgery	0 (0.0)	10 (9.7)	10 (4.9)	0.0016
Asthma	7 (6.9)	0 (0.0)	7 (3.4)	0.0068
Infection	21 (20.6)	12 (11.7)	33 (16.1)	0.0817
CCI, mean (SD)	0.9 (1.1)	1.1 (1.4)	1.0 (1.3)	0.2057
APACHE II score, mean (SD)	16.9 (7.7)	16.9 (6.6)	16.9 (7.2)	0.9853
APACHE II score, median	18	17	18	

Notes: * – p-value < 0.05; ** – p-value < 0.01; *** – p-value < 0.001; **** – p-value < 0.0001. Abbreviations: CAM – Confusion Assessment method; GCS – Glasgow Coma Scale/Score; ICU – Intensive Care Unit; kg – kilograms; SD – standard deviation. APACHE II – Acute Physiology And Chronic Health Evaluation II. a) Based on American heart association definition); b) Based on 1 positive CAM-ICU Scores; c) sedation of Ketamine or Propofol and Fentanyl, depending on the study group of Intervention or control, respectively.

nosis of asthma, there were 6.9% in the K-G compared to 0% in the PF-G (p-value=0.0068) (Table 1).

There was no statistically significant difference with the incidence of midazolam (32.4% compared to 42.7%, p-value=0.1255) or dexmedetomidine use (66.7% compared to 57.3%, p-value=0.1664) between the intervention and control group, respectively (Table 2).

For the primary outcome, there were reduced vasopressor requirements as measured by norepinephrine doses in K-G versus PF-G after ketamine initiation. Up to 12 hours prior to time 0 hour, the average norepinephrine dose was similar between K-G and PF-G, 10.3 mcg/kg/min vs 10.3 mcg/kg/min (p-value=0.9962). The average dose of norepinephrine was lower up to 48 hours after the initiation of ketamine (K-G) compared to PF-G, 8.7 mcg/kg/min vs 14.2 mcg/kg/min (p-value=<0.0001) (Table 3). This associated reduction in average norepinephrine dose was consistent when looking at the time intervals of 12 hours (11.7 mcg/kg/min vs 13.3 mcg/kg/min, p-value=0.0267), 13-24 hours (8.8 mcg/kg/min vs 14.3 mcg/kg/min, p-value=<0.0001), 25-36 hours (7.4 mcg/kg/min vs 13.5 mcg/kg/min, p-value=<0.0001), and 37-48 hours (6.7 mcg/kg/min vs 16.1 mcg/kg/min, p-value=<0.001) (Table 3, Figure 2) after time 0 hour. Figure 3 shows the average dose of norepinephrine

hourly, starting 12 hours before and 48 hours after the initiation of ketamine or propofol/fentanyl.

There was no associated difference in all-cause mortality, 30-day mortality, in-hospital mortality, ICU mortality, ICU LOS, and ventilator-free days between the K-G and PF-G (Table 4). The all-cause, 30-day, ICU, and in-hospital mortality rates were similar in both groups (with overall rates of 32.2%, 21.5%, 22%, 23.9%, p-value=0.8019, 0.9709, 0.8952, 0.8392, respectively). Overall average ICU and hospital LOS were 8.8 days (p-value=0.5174) and 16.6 days (p-value=0.9280), respectively. The average ventilator free days was 23.0 (SD=5.3) (p-value=0.5667).

DISCUSSION

Ketamine has a long history of clinical use and its application is steadily widening due to ongoing challenges with sedation in patients that do not respond to conventional therapy or have side effects with standard drug regimens. As a drug with sedative and analgesic properties and a favorable hemodynamic profile, the potential physiological benefits of ketamine in critically-ill patients undergoing mechanical ventilation may be under-appreciated. According to animal studies, the mechanism of increased

Table 2. Sedative medications while in ICU.

Medication name	Study group		Overall (n=205)	P-value
	Intervention group 49.8% (n=102)	Control group 50.2% (n=103)		
Ketamine, no. (%)	102 (100.0)	0 (0.0)	102 (49.8)	<0.0001
Propofol, no. (%)	82 (80.4)	103 (100.0)	185 (90.2)	<0.0001
Fentanyl, no. (%)	53 (52.0)	103 (100.0)	156 (76.1)	<0.0001
Dexmedetomidine, no. (%)	68 (66.7)	59 (57.3)	127 (62.0)	0.1664
Benzodiazepine (Midazolam), no. (%)	33 (32.4)	44 (42.7)	77 (37.6)	0.1255

Notes: * – p-value < 0.05; ** – p-value < 0.01; *** – p-value < 0.001; **** – p-value < 0.0001. Sedation with ketamine or propofol and fentanyl, depending on the study group of intervention or control, respectively.
Abbreviations: ICU – Intensive Care Unit.

Table 3. ICU Norepinephrine (12 hours before, and up to 48 hours after starting on sedative(s)).

Medication name	Study group		Overall (n=205)	P-value
	Intervention group 49.8% (n=102)	Control group 50.2% (n=103)		
Norepinephrine (before or after started on sedative(s)), no. (%)**	59 (57.8)	37 (35.9)	96 (46.8)	0.0017
Average dose (mcg/kg/min)****, Mean (SD)	9.0 (2.9)	13.5 (3.3)	11.3 (3.8)	<0.0001
Norepinephrine up to 12 hours before started on sedative(s), no. (%)**	38 (37.3)	20 (19.6)	58 (28.4)	0.0052
Average dose (mcg/kg/min), Mean (SD)	10.3 (3.7)	10.3 (2.6)	10.3 (3.1)	0.9962
Norepinephrine up to 48 hours after started on sedative(s), no. (%)**	52 (52.5)	35 (34.0)	87 (43.1)	0.0078
Average dose (mcg/kg/min)****, Mean (SD)	8.7 (2.6)	14.2 (3.0)	11.5 (4.0)	<0.0001
Norepinephrine up to 12 hours after started on sedative(s), no. (%)	47 (46.1)	34 (33.0)	81 (39.5)	0.0557
Average dose (mcg/kg/min)*, Mean (SD)	11.7 (1.4)	13.3 (1.9)	12.5 (1.8)	0.0267
Norepinephrine 13-24 hours after started on sedative(s), no. (%)**	41 (40.2)	24 (23.2)	65 (31.7)	0.0093
Average dose (mcg/kg/min)****, Mean (SD)	8.8 (1.7)	14.3 (3.2)	11.5 (3.7)	<0.0001
Norepinephrine 25-36 hours after started on sedative(s), no. (%)	31 (30.4)	22 (21.4)	53 (25.9)	0.1397
Average dose (mcg/kg/min****), Mean (SD)	7.4 (2.3)	13.5 (3.4)	10.5 (4.2)	<0.0001
Norepinephrine 37-48 hours after started on sedative(s), no. (%)	24 (23.5)	18 (17.5)	42 (20.5)	0.2829
Average dose (mcg/kg/min) ****, Mean (SD)	6.7 (1.5)	16.1 (3.0)	11.4 (5.3)	<.0001

Notes: * – p-value < 0.05; ** – p-value < 0.01; *** – p-value < 0.001; **** – p-value < 0.0001. Sedation with ketamine or propofol and fentanyl, depending on the study group of intervention or control, respectively.

sympathetic response of ketamine may be related to the tissue release of catecholamine stores. Chang et al. demonstrated in rats that the increased blood pressure effect by ketamine was blunted by pretreatment with reserpine, which depletes tissues catecholamines.[27]

We observed a persistent decrease in average norepinephrine doses up to 48 hours after the initiation of ketamine as compared to patients who received fentanyl and propofol. We categorized the average doses based on different time intervals and the reduction in average doses was consistent. Previous studies reported effects of this vasopressor response up to 24 hours, our findings show a longer effect up to 48 hours.[16,17] This prolonged effect

suggests there may be additional mechanisms to this vasopressor response besides release of tissue catecholamines. There may be a direct vasoconstrictive effect increasing systemic vascular resistance (SVR).

The benefits of ketamine in mechanically-ventilated patients may extend beyond the sympathomimetic properties. Although not yet studied in a randomized trial, the bronchodilatory properties and improvement of dynamic compliance have led many clinicians to consider and use ketamine infusions in asthmatic patients.[28] To our knowledge, no clear dose or duration of ketamine-related bronchodilation have been published. A study by Heshmati et al. examined asthmatic patients who did not
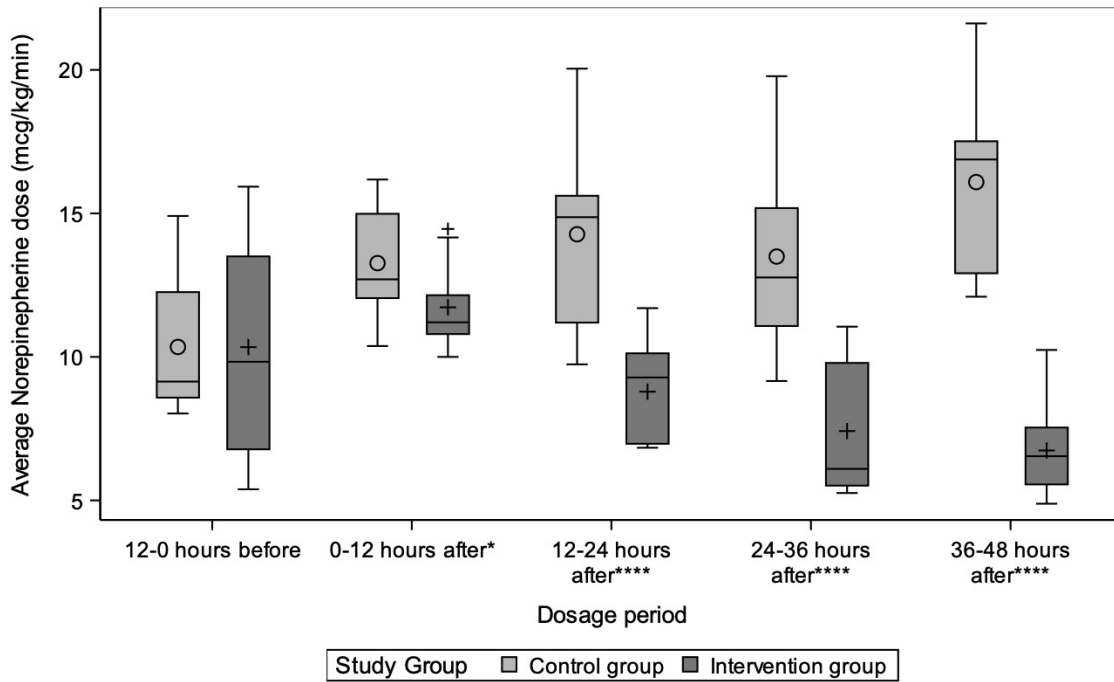
Figure 2. Summary of Norepinephrine dose (mcg/kg/min) usage by period and study group.

Notes: * – p-value < 0.05; ** – p-value < 0.01; *** – p-value < 0.001; **** – p-value < 0.0001. Sedation of Ketamine or Propofol and Fentanyl, depending on the study group of Intervention or control, respectively.

Table 4. Secondary Outcomes

	Study group			
	Intervention group 49.8% (n=102)	Control group 50.2% (n=103)	Overall (n=205)	
Any time all-cause mortality	32 (31.4)	34 (33.0)	66 (32.2)	0.8019
30-day all-cause mortality	22 (21.6)	22 (21.4)	44 (21.5)	0.9709
In-hospital all-cause mortality	25 (24.5)	24 (23.3)	49 (23.9)	0.8392
In-ICU all-cause mortality	22 (21.6)	23 (22.3)	45 (22.0)	0.8952
LOS (in days), Mean (SD)	16.7 (15.8)	16.5 (21.7)	16.6 (19.0)	0.9280
ICU LOS (in days), Mean (SD)	9.2 (7.4)	8.4 (10.6)	8.8 (9.1)	0.5174
Ventilator-free days[a], Mean (SD)	22.8 (5.7)	23.2 (4.9)	23.0 (5.3)	0.5667

Notes: * – p-value < 0.05; ** – p-value < 0.01; *** – p-value < 0.001; **** – p-value < 0.0001; a – Ventilator-free days were defined based on days free of the ventilator within 28 days. Patients on the ventilator for more than 28 days were considered to have 0 ventilator-free days. Abbreviations: ICU – intensive care unit; IV – intravenous; LOS – length of stay; SD – standard deviation.

respond to traditional therapy and on mechanical ventilation after 24 hours, the addition of continuous ketamine infusion for two hours demonstrated a decreased mean peak airway pressure and arterial CO2.[29] This perceived benefit may have affected the use of ketamine in our patient groups as we found that all patients with the primary diagnosis of asthma were observed to be managed with continuous ketamine infusion.

However, ketamine may not be suitable for all intubated patients and especially those with heart failure. Animal models have shown dose-related myocardial depression, with higher doses correlating with lower cardiac output.[27] A randomized study revealed a decrease in cardiac index with ketamine in patients with reduced left ventricular function in the first 24 hours. Pulmonary capillary wedge pressure and mean pulmonary artery pressure were elevated as well. The SVR was higher in the ke-

tamine group. It remains unclear if this is the effect of direct suppression of the myocardium or the result of the increased afterload.[30]

There are several limitations to our study. The first is the nature of its retrospective design. We found an associated decrease in vasopressor use, however this does not prove that the reduced vasopressor dose was caused by the ketamine use. These results should be considered hypothesis-generating. Second, finding a control group to match the study group was a challenge, as ketamine can be used with any number or combination of sedation agents. We chose two sedation agents that were commonly used clinically, however the 2 groups were likely managed quite differently from one another. We also did not specifically examine the sedating agents used during intubation which may have affected the initial blood pressures and vasopressor needs.
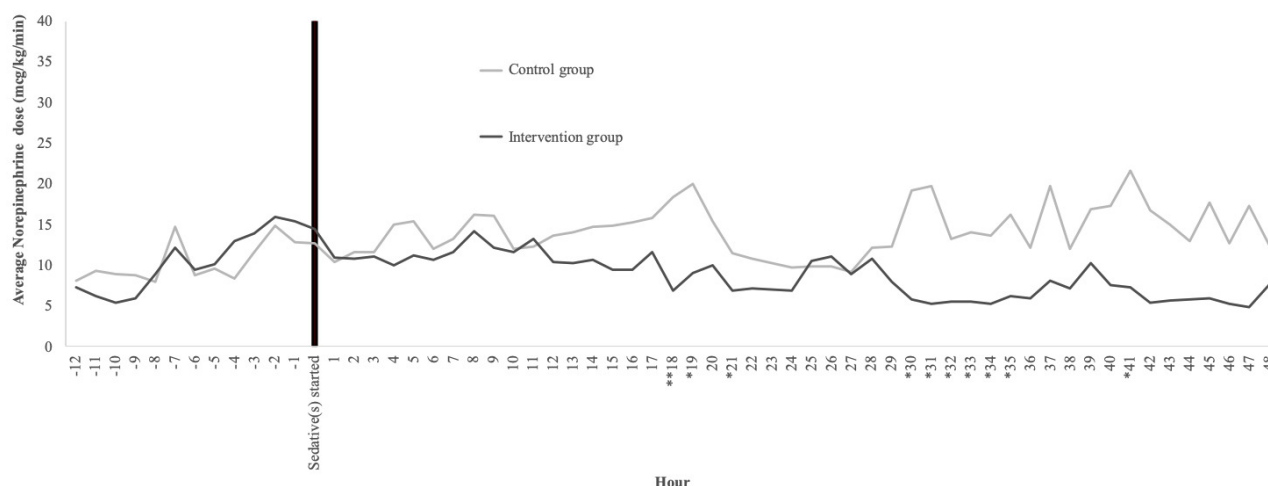
Figure 3. Average Norepinephrine dose (mcg/kg/min) usage by hour and by study group.

Notes: * – p-value < 0.05; ** – p-value < 0.01; *** – p-value < 0.001; **** – p-value < 0.0001. Sedation of Ketamine or Propofol and Fentanyl, depending on the study group of Intervention or control, respectively.

As stated earlier, asthmatic patients had markedly more use of ketamine and it can also be observed that ketamine was not used at all in the trauma and surgical patients in this study. The perceived cardiopulmonary benefits of ketamine on asthma patients likely led to more asthma patients receiving ketamine and may have skewed the overall results to favor the ketamine group. While a MAP of 65 mmHg was most often used in our institutions, there was no standardized blood pressure target in this study adding provider-related variation with this. Also, multiple vasopressors may have been used but we examined norepinephrine specifically as it is the predominant vasopressor used at our institution. Use of other vasopressors was not accounted for in this study.

CONCLUSION

In our retrospective study, we demonstrated the use of ketamine as an adjunct for sedation in mechanically ventilated patients was associated with decreased vasopressor requirements when compared to a common sedation regimen of propofol and fentanyl. Further research with multicenter, randomized, placebo-controlled trials are required to better define the role of ketamine as an adjunct sedation agent for critically-ill patients on mechanical ventilation.

Acknowledgement

N/A

Corresponding author

Gerardo Carino MD, PhD
Associate Professor of Medicine, Clinician Educator
Division of Pulmonary, Critical Care and Sleep Medicine
Warren Alpert Medical School at Brown University,
164 Summit Avenue, Providence, RI, 02906, USA
Tel: 401-793-4501
Fax: 401-793-4511
Email: Gerardo_Carino@brown.edu

REFERENCES

1. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. *Clin Pharmacol Ther*. 1965;6(3):279-291. doi:10.1002/cpt196563279

2. Haley-Andrews S. Ketamine: the sedative of choice in a busy pediatric emergency department. *J Emerg Nurs*. 2006;32(2):186-188. doi:10.1016/j.jen.2005.12.051

3. Dahmani S, Michelet D, Abback PS, et al. Ketamine for perioperative pain management in children: a meta-analysis of published studies. *Paediatr Anaesth*. 2011;21(6):636-652. doi:10.1111/j.1460-9592.2011.03566.x

4. American College of Emergency Physicians. Optimizing the Treatment of Acute Pain in the Emergency Department. Published online 2017.

5. Gharaei B, Jafari A, Aghamohammadi H, et al. Opioid-sparing effect of preemptive bolus low-dose ketamine for moderate sedation in opioid abusers undergoing extracorporeal shock wave lithotripsy: a randomized clinical trial. *Anesth Analg*. 2013;116(1):75-80. doi:10.1213/ane.0b013e31826f0622

6. Guillou N, Tanguy M, Seguin P, Branger B, Campion JP, Mall??dant Y. The effects of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. *Anesth Analg*. 2003;97(3):843-847. doi:10.1213/01.ane.0000075837.67275.36

7. Price RB, Iosifescu DV, Murrough JW, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. *Depress Anxiety*. 2014;31(4):335-343. doi:10.1002/da.22253

8. Miller AC, Jamin CT, Elamin EM. Continuous intravenous infusion of ketamine for maintenance sedation. *Minerva Anestesiol*. 2011;77(8):812-820.

9. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-306. doi:10.1097/ccm.0b013e3182783b72

10. Saugel B, Bebert EJ, Briesenick L, et al. Mechanisms contributing to hypotension after anesthetic induction with sufentanil, propofol, and rocuronium: a prospective observational study. *J Clin Monit Comput*. 2021;36(2):341-347. doi:10.1007/s10877-021-00653-9

11. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA*. 2012;307(11):1151-1160. doi:10.1001/jama.2012.304

12. Jenkins CR, Gomersall CD, Leung P, Joynt GM. Outcome of patients receiving high dose vasopressor therapy: a retrospective cohort study. *Anaesth Intensive Care*. 2009;37(2):286-289. doi:10.1177/0310057x0903700212

13. Brown SM, Lanspa MJ, Jones JP, et al. Survival after shock requiring high-dose vasopressor therapy. *Chest*. 2013;143(3):664-671. doi:10.1378/chest.12-1106

14. Roberts RJ, Miano TA, Hammond DA, et al. Evaluation of Vasopressor Exposure and Mortality in Patients With Septic Shock. *Crit Care Med*. 2020;48(10):1445-1453. doi:10.1097/ccm.0000000000004476

15. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. *Anesth Analg*. 1966;45(1):29-40. doi:10.1213/00000539-196601000-00007

16. Garber PM, Droege CA, Carter KE, Harger NJ, Mueller EW. Continuous Infusion Ketamine for Adjunctive Analgosedation in Mechanically Ventilated, Critically Ill Patients. *Pharmacotherapy*. 2019;39(3):288-296. doi:10.1002/phar.2223

17. Buchheit JL, Yeh DD, Eikermann M, Lin H. Impact of Low-Dose Ketamine on the Usage of Continuous Opioid Infusion for the Treatment of Pain in Adult Mechanically Ventilated Patients in Surgical Intensive Care Units. *J Intensive Care Med*. 2019;34(8):646-651. doi:10.1177/0885066617706907

18. Reese JM, Sullivan VF, Boyer NL, Mount CA. A Non-Comparative Prospective Pilot Study of Ketamine for Sedation in Adult Septic Shock. *Mil Med*. 2018;183(11-12):e409-e413. doi:10.1093/milmed/usy121

19. Nuttall FQ. Body Mass Index: Obesity, BMI, and Health: A Critical Review. *Nutr Today*. 2015;50(3):117-128. doi:10.1097/nt.0000000000000092

20. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;2(7872):81-84. doi:10.1016/s0140-6736(74)91639-0

21. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941-948. doi:10.7326/0003-4819-113-12-941

22. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829. doi:10.1097/00003246-198510000-00009

23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8

24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010

25. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. doi:10.1016/j.jbi.2019.103208

26. The code/data analysis for this paper was generated using SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2021 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

27. Chang P, Chan KE, Ganendran A. Cardiovascular effects of 2-(O-chlorophenyl)-2-methylaminocyclohexanone (CI-581) in rats. *Br J Anaesth*. 1969;41(5):391-395. doi:10.1093/bja/41.5.391

28. Youssef-Ahmed MZ, Silver P, Nimkoff L, Sagy M. Continuous infusion of ketamine in mechanically ventilated children with refractory bronchospasm. *Intensive Care Med*. 1996;22(9):972-976. doi:10.1007/bf02044126

29. Heshmati F, Zeinali MB, Noroozinia H, et al. Use of ketamine in severe status asthmaticus in intensive care unit. *Iran J Allergy Asthma Immunol*. 2003;2(4):175-180.

30. Christ G, Mundigler G, Merhaut C, et al. Adverse cardiovascular effects of ketamine infusion in patients with catecholamine-dependent heart failure. *Anaesth Intensive Care*. 1997;25(3):255-259. doi:10.1177/0310057x9702500308