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Ketamine infusion as a sedative-analgesic in severe ARDS (KISS)

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ABSTRACT

Rationale

Ketamine has been used as a sedative analgesic in trauma setting, but data regarding its efficacy and safety is lacking in severe ARDS. This retrospective study aims to determine if Ketamine is safer as a sedative agent in mechanically ventilated patients. During the COVID pandemic, as there was a shortage of sedative agents, Ketamine was used.

Objectives

The primary objective was to compare the safety of ketamine to other sedatives. The secondary objective was to compare the effect of ketamine to other sedatives regarding the need for vasopressor, incidence of delirium, infectious complications, acute kidney injury, hospital length of stay, and length of ventilator days.

Methods

A retrospective, observational cohort study was conducted.

Measurements and Main Results

One hundred and twenty-four patients (63 men and 61 women) were included. Thirty-four patients received ketamine, while 90 patients received other traditionally used sedatives such as propofol and midazolam. The patients' median age was 64 years in the ketamine group and 68 years in the non-ketamine group. Seventeen patients in the ketamine group (50%) and 65 patients (72%) in the non-ketamine group had mortality (p < 0.02). The hospital length of stay was 22.85 days (± 16.36) in the ketamine group and 15.62 days (± 14.63) in the non-ketamine group (p < 0.02). There was no statistically significant difference among the outcomes of the need for vasopressor, the incidence of delirium, infectious complications, and acute kidney injury.

Conclusions

Ketamine as a sedative-analgesic agent in COVID-19 patients with severe acute respiratory distress syndrome demonstrated safety with reduced mortality. The ketamine group had a higher hospital length of stay, but a similar complication profile compared to the non-ketamine group. Further prospective randomized controlled trials are warranted to confirm these findings.

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1. Background

Coronavirus disease 2019 (COVID-19) pandemic impacted the healthcare of the USA drastically. In the USA, New York City had the greatest impact during the early pandemic phase. COVID-19 presents with a spectrum of symptoms ranging from an

asymptomatic and mild illness that can be managed safely at home to critical illness requiring intensive care unit (ICU) admission. During the early phases of the pandemic, prior to well-defined treatment options, many COVID-19 patients with critical illness required respiratory support with a high percentage of patients requiring invasive ventilation [1]. There was an overwhelming requirement of ventilators, at times even leading to concern for shortage [2]. In New York City, 12.3–33.1% of patients with COVID-19 required mechanical ventilation [3]. Sedative analgesics are indicated in patients with respiratory failure who are on mechanical ventilators [4]. Commonly used sedative analgesics are benzodiazepines (e.g., diazepam, lorazepam, midazolam), opioid analgesics (e.g., fentanyl, hydromorphone, morphine, remifentanil), propofol and dexmedetomidine [5]. With the high demand for mechanical ventilators, there was also a shortage of sedatives and analgesics utilized in mechanically ventilated patients [1,4]. This situation mandated the clinicians to find alternative approaches for sedation, analgesia, and paralysis for ventilated COVID-19 patients [1]. Our ICU faced shortage of dexmedetomidine, remifentanil, and other anesthetics. Hence, ketamine was used for analgesio-

sedation although it has not been extensively validated in critically ill patients on mechanical ventilators. The choice of ketamine was decided primarily by the treating physicians based on the availability during that circumstance, and no specific criteria

were used. However, a premorbid psychosis or history of post-traumatic stress disorder was considered a relative contraindication for ketamine [6].

Ketamine is a dissociative anesthetic with analgesic, anti-inflammatory, and amnestic properties. In addition, ketamine has neuroprotective effects and some anticonvulsant properties. Probably, ketamine is the only sedative agent that preserves hemodynamics [7]. Ketamine is typically used in trauma settings due to its combined sedation and analgesia together with favorable effects on hemodynamics and uncommonly used to treat refractory bronchospasm and depression [7,8]. Ketamine, through its effect on the sympathetic nervous system, increases heart rate, blood pressure, and cardiac output which makes it an excellent choice for intravenous induction in patients with hypotension or shock in emergency settings [7]. Ketamine is the preferred

anesthetic when the supply of oxygen, monitoring, and other disposable equipment is limited, given the relative sparing of spontaneous respiration. Despite many benefits of ketamine, its use remains limited in ICU settings because of the lack of extensive data regarding its safety, association with emergence reactions in ICU patients, and increasing recognition as a drug with potential for abuse.

The primary objective was to compare the safety of ketamine to other sedatives in mechanically ventilated patients. The secondary objective was to compare the effect of ketamine to other sedatives regarding the need for vasopressor, incidence of delirium, infectious complications, acute kidney injury, hospital length of stay (LOS), and length of ventilator days.

2. Methods

2.1. Study design, inclusion and exclusion criteria

A retrospective, observational cohort study was designed to compare the safety of ketamine as a sedative analgesic agent to other agents. Ketamine was predominantly used during the early phase of COVID pandemic, when there was a shortage of the traditional ICU sedatives.

Inclusion criteria included
- all patients between 18 and 90 years of age,
- moderate to severe acute respiratory distress syndrome (ARDS) due to COVID-19 with an arterial partial pressure of oxygen divided by the inspired oxygen concentration (P/F) ratio <150 with a minimum 5 cm of positive end-expiratory pressure on a mechanical ventilator.

Exclusion criteria included
- post-cardiac arrest status,
- premorbid diagnosis of dementia,
- dependency on extra-corporeal therapies prior to or during ICU stay.

The study was approved by the hospital ethics committee and institutional review board. The study was categorized as minimal risk, with a waiver of consent given the retrospective nature of the study.

Following inclusion and exclusion criteria, medical records were reviewed of all eligible patients. Patients were allotted to one of the two groups: those who received ketamine and those who did not receive ketamine. Hospital LOS was the time from the date of admission till the date of discharge.

3. Duration of study

All adult patients admitted to the intensive care unit of an academic community hospital from

February 2020 to November 2020 were included in the study.

4. Pharmacologic agents and sedation monitoring

Standard of Care practices with critical care bundles were followed. Sedation was scored by the nurses using the Richmond agitation sedation scale (RAAS). A target RAAS of −3 to −4 was used for patients with moderate ARDS, and a target RAAS of −5 was used for patients with severe ARDS or if the patients had elevated respiratory drive. A second agent was added if the target was not achieved with a single agent.

Paralytics and prone positions were applied as per the ARDS net guidelines, and a target RAAS score of −5 was achieved before these maneuvers. Daily weaning and awakening trials were performed. Vasopressors and inotropes were chosen based on dominating pathophysiology determined by bedside ultrasound and surviving sepsis three guidelines if the patient was in septic shock .

Ketamine was started with a loading dose of 0.5 mg/kg intravenous bolus followed by 0.5 mg/kg/hr via continuous infusion. The rate was titrated within the range of 0.2 to 1 mg/kg/hr to achieve target RAAS.

Propofol was started at an initial dose of 5 mcg/kg/min intravenous, increased by increments of 5

mcg/kg/min every 10 minutes up to a maximum of 50 mcg/kg/min. It was discontinued if refractory hypotension or elevated triglycerides > 700 mg/dL, which were obtained every 48 hours.

Midazolam was started with a bolus dose of 4 mg intravenous push followed by an infusion rate ranging from 0.01 to 0.1 mg/kg/hr. Opioids included fentanyl 100–200 mcg every 3 hours intravenous bolus or hydromorphone 2–4 mg intravenous every 6 hours.

Steroids were used based on the prevailing guidelines. Some considerations included hydrocortisone 50 mg intravenous every 6 to 8 hours for refractory septic shock, methylprednisolone 1–2 mg/kg for chronic obstructive pulmonary disease/asthma exacerbation, dexamethasone 10 mg intravenous for ARDS without pneumonia.

5. Statistical analysis

We analyzed the de-identified data using statistical analytical software (version 9.4 M7). All continuous variables were reported as median ± standard deviation, while categorical variables were reported as percentages. A p-value of <0.05 was considered as the cutoff for statistical significance when comparing the two groups.

6. Results

A total of 124 patients were included in this study of whom 34 patients received ketamine while

90 patients received other traditionally used sedatives such as propofol and midazolam (Table 1). The patients'

median age in both the groups was comparable, in the ketamine group being 64, and in the non-ketamine group being 68. The percentage of male patients in the ketamine vs. non-ketamine group was 65% vs. 46%.

A statistically significant difference in all-cause mortality was noted between the two groups. In the ketamine group, 17 of 34 patients (50%), while in the non-ketamine group, 65 (72%) of 90 patients had mortality as an outcome (p < 0.02). Although the ketamine group had lower all-cause mortality, an increase in hospital LOS was noted. Hospital LOS in the ketamine group was 22.85 days (± 16.36), and in the non-ketamine group, hospital LOS was 15.62 days (± 14.63) (p < 0.02).

Comparing the two groups for premorbid conditions, a significant difference in seizure history between the two groups is noted. Five patients (15%) had a history of seizures in the ketamine group, while three patients (3.33%) had a history of seizure disorder in the non-ketamine group. No significant differences were noted for other premorbid conditions of pulmonary embolism, congestive heart failure, obesity, hypertension, and diabetes mellitus (Table 1). When other complication outcomes were compared between the two groups, there was no statistically significant difference among the outcomes of need for vasopressor use, delirium, catheter-associated urinary tract infection, bloodstream infections, ventilator-associated pneumonia, and acute kidney injury between ketamine and non-ketamine group (Table 1).

Table 1. Outcomes and co-morbidities of ketamine and non-ketamine group.

Variable	Ketamine group (n = 34)	Non-ketamine group (n = 90)	p-value
Outcomes			
Mortality	17 (50%)	65 (72%)	0.02
Need for vasopressor	18 (53%)	60 (67%)	0.16
Delirium	3 (9%)	3 (3.3%)	0.20
Hospital length of stay	22.85 + 16.36	15.62 + 14.63	0.02
Ventilator days	14.24 + 14.53	10.03 + 11.63	0.10
Of the surviving discharges –	**(n = 17)**	**(n = 25)**	
Discharge with disability on ventilator	3 (18%)	3 (12%)	0.61
Discharge outside hospital	13 (76%)	23 (92%)	0.16
Infectious complications			
Catheter-associated urinary tract infection	7 (21%)	15 (17%)	0.61
Bloodstream infection	5 (15%)	26 (29%)	0.10
Ventilator-associated pneumonia	12 (35%)	26 (29%)	0.49
Acute kidney injury	23 (68%)	60 (67%)	0.92
Comorbidities			
Pulmonary embolism	4 [11]	3 [3]	0.07
Congestive heart failure	9 (27)	16 (18)	0.27
Obesity	12 (35)	37 (41)	0.59
Seizure	5 (15)	3 [3]	0.02
Chronic obstructive pulmonary disease/asthma	5 (15%)	15 (17%)	0.81
Hypertension	23 (68%)	71 (78%)	0.35
Diabetes mellitus	19 (56%)	63 (69%)	0.16
Male gender	22 (65%)	41 (46%)	0.06
Age	64.4 + 13.4	68.1 + 14.0	0.19

7. Discussion

Our study found statistically significant lower mortality in the ketamine group compared to the non-ketamine group. The baseline characteristics of the two groups in this study were comparable and cannot explain the mortality difference. Currently, the pathophysiological mechanisms resulting in survival benefit remain unclear. We hypothesize that these may include antioxidant and anti-inflammatory properties of ketamine. While there is some suggestion from animal studies that racemic ketamine may have anti-inflammatory effects, human studies remain controversial. One study assessing the antidepressant property of ketamine reported a transient (mostly hours) decrease in inflammatory mediators such as interleukin-6 and interleukin-1 alpha following ketamine treatment [9]. In this study, the anti-inflammatory property did not correlate with antidepressant response, but changes in fibroblast growth factor-2 correlated with antidepressant response. Another study reported that a rapid decrease in the pro-inflammatory mediator, tumor necrosis factor-alpha, correlated with rapid antidepressant effects of ketamine, suggesting that the impact of ketamine on inflammatory cytokines [10,11].

The RECOVERY trial has undoubtedly established the protective role of anti-inflammatory agents such as dexamethasone and tocilizumab (anti-interleukin -6) in selected COVID-19 patients [12]. Extrapolating the essence of the above studies analyzing ketamine as an antidepressant, it is plausible the ketamine may have a survival benefit because of these antiinflammatory properties given its plummeting effect on both inflammatory and pro-inflammatory markers. Our study also found no differences in the incidence of infectious complications between the two groups. This suggests that the anti-inflammatory effects of ketamine may not necessarily lead to immunosuppression.

The hospital LOS was significantly higher in the ketamine group compared to the non-ketamine group. This difference in length of stay could be explained by the neurocognitive perturbation by ketamine. Of note, the delirium rates between the two groups in our study were similar, possibly because of the timing of delirium assessment. Delirium scoring was drafted in our study only after extubation and not while receiving mechanical ventilation. It may be expected that some patients might have well been out of delirium by the time of extubation.

This study's limitations include small sample size, retrospective observational nature of the study, and the specific subset of COVID-19 patients with severe ARDS that was under study. These findings require further confirmation with prospective randomized controlled trials in other mechanically ventilated patients. Nevertheless, this study highlights the role and benefits of ketamine as a sedative analgesic in severe ARDS patients affected with COVID-19. Ketamine appears at least a safer alternative to the traditional agents, perhaps with a mortality benefit in patients who many require anti-inflammatory therapy.

8. Conclusion

Ketamine as a sedative analgesic in COVID-19 patients with severe ARDS demonstrated safety with reduced mortality. The ketamine group did have a higher hospital LOS, but a similar complication profile compared to the non-ketamine group. Further prospective randomized controlled trials are warranted to confirm these findings.

Author contribution statement

Ramakanth Pata, MD
Contributions: Conception and design, Acquisition of data, Analysis and interpretation of data, drafting or revising the article.

Pagali Sandeep, MD Contributions: Analysis and interpretation of data, drafting or revising the article.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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