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Ketamine as a Supplementary Analgosedative in COVID-19 Patients on Mechanical Ventilation: A Single-Center Observational Study

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ABSTRACT

Introduction: Sedation of coronavirus disease-2019 (COVID-19) acute respiratory distress syndrome (ARDS) patients on mechanical ventilation (MV) has lately become a concern. The purpose of this study was to report the sedation strategy used in COVID-19 ARDS patients who were mechanically ventilated at a single institution.

Methods: In this study, we performed a retrospective review of the sedation strategy in mechanically ventilated COVID-19 ARDS patients in our 37-bed intensive care unit. All mechanically ventilated COVID-19 ARDS patients who were sedated and hospitalized between March 2020 and September 2021 were included in this study. Patients reported using sedatives and analgesics as well as suffering from delirium.

Results: This study involved 100 patients with COVID-19 ARDS who were both eligible to participate. In all patients, a triple sedation regimen was required. Ketamine attitudes reduced patients' opioid and benzodiazepine needs ($p<0.05$). Furthermore, the following ketamine administration, the need for vasopressors was significantly reduced ($p<0.05$). There were no drug interactions documented.

Conclusion: We showed that extremely high sedative doses were required in this group of patients with COVID-19 ARDS who needed MV. However, our findings suggest that when ketamine infusion was introduced, benzodiazepine, opiate, and vasopressor doses were reduced without adverse pharmacological effects. Further research will be required to determine appropriate dosing regimens.

Keywords: Ketamine, sedation, ARDS, COVID-19, mechanical ventilation

Introduction

About 5% of coronavirus disease-2019 (COVID-19) infections progress to acute respiratory distress syndrome (ARDS), which frequently necessitates intubation and invasive mechanical ventilation (MV) (1). Unusually high doses of sedative and analgesic drugs are often used in patients with COVID-19 ARDS to alleviate anxiety, reduce excessive oxygen use, and enhance treatment (2). Although routinely used sedatives and analgesics are beneficial for many patients, they are associated with several side effects, including opioid-induced constipation and hemodynamic instability associated with propofol and dexmetatomidine (3,4).

To the best of our knowledge, only a few trials have been undertaken to target sedation in COVID-19 ARDS patients. Wongtangman et al. (2) reported that ARDS patients with COVID had a much higher need for analgosedation based on a sedative burden index. Furthermore, Kapp et al. (5) showed a link between deep sedation and death in mechanically ventilated COVID-ARDS patients.

Ketamine, a non-competitive NMDA receptor antagonist, induces sleepiness, amnesia, and analgesia while preserving pulmonary compliance and lowering airway resistance (6-8). Thus, ketamine provides an additional sedative option in COVID-19-induced ARDS patients. We anticipated in this study that continuous ketamine infusion would minimize sedative and analgesic consumption and the prevalence of delirium in COVID-19-induced ARDS patients.

Methods

Study Design and Setting

This is a single-center, retrospective observational study conducted in a 37-bed multidisciplinary academic intensive care unit (ICU) that serves between 900 and 950 inpatients each year. The study protocol was evaluated and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2390, date: 29.05.2020). Our unit has a physician-driven

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institutional strategy, aiming for a sedation state of 2 to +1 on the Richmond Agitation Sedation Scale (9).

We used a first-line sedation approach comprising continuous infusion of an opioid (fentanyl, starting dosage 0.7 mcg/kg/h), a benzodiazepine (midazolam, starting dose 0.03 mg/kg/h), or a combination of both, depending on the clinical features of the patients and the projected illness course. When high opioid and benzodiazepine dosages (e.g., fentanyl 3 mcg/kg/h, midazolam 0.1 mg/kg/h) failed to provide appropriate analgosedation, ketamine was delivered as a continuous infusion at a dose of 10 mg/kg/min. Daily, bedside nurses employed the confusion assessment technique for ICU (CAM-ICU) to track the occurrence of delirium (10).

Study Population

We included all patients who had positive severe acute respiratory syndrome-coronavirus-2 polymerase chain reaction results and required invasive MV for ARDS between March 2020 and September 2021. Patients who were pregnant or breastfeeding, had psychosis as defined by the DSM-IV, were given a concomitant neuromuscular blocker, regularly used opiates, or were administered ketamine on the first day of MV were excluded from the study. Patients were treated for COVID-19 as per local guidelines.

Data Collection

A retrospective query of the institutional electronic system and medical documents was conducted to collect data for this study. The following variables were gathered: 1) demographic information such as age, gender, and weight; 2) clinical baseline features such as comorbidities, Acute Physiologic and Chronic Health Evaluation II Score, and Sequential Organ Failure Assessment score; 3) ICU stay metrics such as MV duration, ICU length of stay, and 28-day mortality; 4) nature and dosages of concurrent continuous infusions of analgesics, sedatives, and vasopressor medications. 5) Any occurrence of withdrawal syndrome or delirium that occurred throughout the ICU stay (delirium in the ICU was recorded through the daily routine assessment of the CAM-ICU evaluation reports), 6) any adverse event (AE) that occurred during ketamine infusion.

Outcome Measures

In our study, ketamine was considered useful as an adjuvant for troublesome sedation if no changes in the doses of other analgesics and sedatives were necessary within 72 h following ketamine infusion. Finally, the safety profile of ketamine was assessed as a secondary goal, with a focus on hypertension, tachycardia, laryngospasm, hypersalivation, emesis, nystagmus, anaphylaxis, and erythema.

Statistical Analysis

There was no statistical power analysis performed before this retrospective investigation. The current investigation is looking back. The data was analyzed using the Statistical Package for the Social Sciences for Windows version 26.0 software package (SPSS, Chicago, IL). The normality of the distribution was determined using the Shapiro-Wilk test. The quantitative data displayed are the mean ± standard deviation and median (interquartile range). The Wilcoxon signed-rank test was used to compare hemodynamic parameters, sedative and analgesic use, and vasopressor usage before and after ketamine infusion. $P<0.05$ was found to be statistically significant.

Results

We identified 125 (of 830 patients who admitted to the unit and mechanically ventilated) mechanically ventilated COVID-19 ARDS patients who satisfied the inclusion criteria during the assessment period. Twenty patients were excluded; 13 of them were administered neuromuscular blockers, 5 patients received ketamine infusions for less than 24 h, and 2 patients had incomplete documentation. The 100 participants in the research were largely men with an average age of 67.1±14.4 years (Table 1).

Adjunctive analgesics and sedatives were reduced without the use of alternative sedatives. After ketamine administration, fentanyl use was significantly reduced at 24 h [4.25±1.56 vs. 2.71±1.56 µg/kg/hour, ($p<0.001$)], 48 h [4.25±1.56 vs. 1.50±1.62 µg/kg/hour, ($p<0.001$)] and 72 h [4.25±1.56 vs. 0.72±1.11 µg/kg/hour, ($p<0.001$)] (Table 2). Midazolam dose was similarly reduced at 24 h [0.21±0.71 vs. 0.14±0.59 mg/kg/hour, ($p=0.007$)], 48 h [0.21±0.71 vs. 0.10±0.47 mg/kg/hour, ($p<0.001$)], 72 h

Table 1. Baseline characteristics and treatment outcomes of patients[a,b]

Variable	All patients (n=100)
Age, years	67.1±14.4
Male, n (%)	70 (70%)
Body mass index, n (%)	
Underweight	2 (2%)
Normal	30 (30%)
Overweight	35 (35%)
Obese	29 (29 %)
Morbid obese	4 (4%)
Comorbidities, n (%)	
Hypertension	45 (45%)
Diabetes	14 (14%)
CHF	30 (30%)
CKD	20 (20%)
APACHE II score	18.3±7.6
SOFA score at ICU admission	7.2±2.9
P/F at ICU admission	170±35.9
Create CL. (mL/min) at ICU admission	79.6±35.9
Vasopressor used, n (%)	34 (34%)
Mechanical ventilation length median (IQR), days	11 (6-18)
ICU length of stay (days)	18.6±12.8
Delirium status, n (%)	15 (12%)
28-day mortality, n (%)	40 (40%)

[a]Data are presented as mean ± standard deviation unless otherwise indicated, [b]N = number of patients on continuous infusion, Body mass index is classified as <18.5 kg/m^2 underweight, 18.5-24.9 kg/m^2 normal weight, 25-29.9 kg/m^2 overweight, 30-39.9 kg/m^2 obese, and >40 kg/m^2 morbidly obese; CHF: Congestive heart failure, CKD: Chronic kidney diseases, PaO_2/FIO_2: Partial pressure of oxygen/fraction of inspired oxygen, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Orgailure Assessment, ICU: Intensive care unit, Create CL: Creatinine clearance, IQR: Interquartile range

[0.21±0.71 vs. 0.09±0.58 mg/kg/hour, (p<0.001)] compared to baseline before ketamine (Table 2).

Table 2 shows the patient's hemodynamic parameters. Heart rate and blood pressure did not considerably change during the experiment. Our study included 65 patients who required vasopressor treatment, 19 who continued to require vasopressors, and 46 who had vasopressors discontinued after 72 h. The norepinephrine dosage was substantially reduced after 24 hours of ketamine therapy [0.12±0.18 vs. 0.09±0.14 µg/kg/min, (p<0.001)], 48 h [0.12±0.18 vs. 0.06±0.17 µg/kg/min, (p<0.001)], 72 h [0.12±0.18 vs. 0.06±0.2 µg/kg/min, (p<0.001)] (Table 3).

Throughout the study, all patients received ketamine infusions at a rate of 10 µg/kg/min. In our patient cohort, we examined an AE that might have been caused by ketamine. There were no documented side effects, and no patients suffered hypersalivation that required atropine therapy.

Delirium in the ICU is associated with diagnostic issues since the patient was unable to engage in the CAM-ICU evaluation. During their ICU stay, 15 (12%) individuals tested positive for delirium.

Discussion

In this trial, patients received significantly lower benzodiazepine, opiate, and vasopressor doses when ketamine was used as part of a multimodal sedation regimen, with no adverse effects. To the best of our knowledge, this is the first trial to demonstrate the benefits of low-dose ketamine infusion in mechanically ventilated COVID-19 ARDS patients.

It has been discovered that obtaining and maintaining enough analgesia before sedation reduces the duration of mechanical breathing, which is generally performed with the use of opioids. In our group of patients, ketamine exhibited an opioid-sparing effect. Our findings are consistent with previous research on low-dose ketamine (11-14). Ketamine is an agonist of the µ, δ, and κ-opioid receptors and an antagonist of the NMDA receptor, which might explain the reduction in opioid consumption (15,16).

According to our findings, ketamine infusion in mechanically ventilated patients reduced not only opioid consumption but also benzodiazepine use without compromising proper sedation. Although no studies have been undertaken to evaluate its effectiveness in describing extreme sedation, ketamine's benzodiazepine-sparing effects are consistent with earlier work addressing moderate sedation techniques (17,18). This is crucial because long-term benzodiazepine infusions have been associated with delirium, long-term cognitive damage, and the need for additional MV time (19,20).

In addition to its positive respiratory dynamics profile, ketamine may have a chronotropic effect on the cardiovascular system via the sympathetic nervous system (15). We noticed a significant reduction in the demand for vasopressors in our patient group. This finding is consistent with a prior study on the use of low-dose ketamine in mechanically ventilated adult patients for moderate sedation (12).

Delirium is crucial in critically ill patients because it is related to diagnostic issues and therapeutic dilemmas, and each additional day

Table 2. Analgesic and sedative dosage needs for continuous infusion before and after ketamine administration[a,b]

Drug	Before Ketamine initiation	24 h after Ketamine initiation	48 h after Ketamine initiation	72 h after Ketamine initiation
Ketamine				
N	0	100	100	100
Dose (µg/kg/min)		10	10	10
Fentanyl				
N	100	100	100	100
Dose (µg/kg/h)	4.25±1.56	2.71±1.56*	1.50±1.62*	0.72±1.11*
Midazolam				
N	100	100	100	100
Dose (mg/kg/h)	0.21±0.71	0.14±0.59*	0.10±0.47*	0.09±0.58*

Wilcoxon signed-rank test was used to test the parameters. [a]Data are presented as mean ± standard deviation unless otherwise indicated, [b]N = number of patients on continuous infusion, *p<0.05 as a comparison of dosing at each specified time point with the original dosing at the time of ketamine initiation

Table 3. Comparison of hemodynamic parameters and vasopressor medications during the analyzed time frame[a,b]

Hemodynamic parameters and medications	Pre-ketamin	24 h after Ketamine initiation	48 h after Ketamine initiation	72 h after Ketamine initiation
SBP, mm Hg	114±18.64	116.00±21.63	106.48±41.86	90.85±58.05
DBP, mm Hg	58.15±11.4	59.61±13.58	54.57±21.06	53.56±24.44
HR, beats per minute	90.76±23.49	87.09±15.43	79±35.53	68±44.03
Noradrenaline				
N	65	30	24	19
Dose (mg/kg/min)	0.12±0.18	0.09±0.14*	0.06±0.17*	0.06±0.2*

HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Wilcoxon signed-rank test was used to test the parameters. [a]Data presented as mean ± standard deviation unless otherwise indicated, [b]N = number of patients on continuous infusion, *p<0.05 as a comprasion of dosing at each specified time point to the original dosing at time of ketamine initiation

of delirium is associated with a 10% increased risk of death (21,22). Dexmetatomidine appears to be producing positive results at the time; nevertheless, it is a more expensive chemical that can induce bradycardia, hypotension, hypertension, nausea, and atrial fibrillation (23,24). Furthermore, studies suggest that ketamine can be used for the treatment of delirium and depression because of its immune-regulatory effects on the peripheral and central nervous systems (25,26). Using the CAM-ICU, 15 patients (15%) tested positive for delirium throughout their ICU stay. This was substantially lower than predicted, given that the frequency of delirium in mechanically ventilated patients admitted to the ICU has been reported to be as high as 24.4% (23,24).

In recent studies, ketamine has been shown to have both proconvulsant and anticonvulsant effects (25). Convulsions were not detected in any of the participants taking ketamine in this trial. Furthermore, ketamine usage has been linked to hypersalivation, which is commonly treated with glycopyrrolate or atropine (26). None of the patients were given medication because of hypersalivation. Some studies highlighted possible adverse effects such as hypertension and tachyarrhythmias, which were not detected in any of the ketamine-treated patients. Lower ketamine doses (10 µg/kg/min) do not appear to produce the psychomimetic side effects observed at higher doses (12).

Study Limitations

The study was conducted at a single location and was retrospective, with no ability to manage treatments to impact analgesic and sedative requirements. However, prospective studies are required to verify these findings and determine the appropriate ketamine dosage in this circumstance.

Conclusion

This study shows that low-dose ketamine has a favorable safety profile, with no significant effects on hemodynamics or agitation. The initiation of ketamine infusion resulted in a significant reduction in the total fentanyl and midazolam requirements, indicating that ketamine as an analgosedative medication could be a viable alternative in mechanically ventilated patients.

Ethics Committee Approval: The study protocol was evaluated and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2390, date: 29.05.2020).

Informed Consent: Retrospective study.

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