# Impact of ketamine as an adjunct sedative in acute respiratory distress syndrome due to COVID-19 Pneumonia

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## ARTICLE INFO

## ABSTRACT

*Purpose:* Deep sedation is sometimes needed in acute respiratory distress syndrome. Ketamine is a sedative that has been shown to have analgesic and sedating properties without having a detrimental impact on hemodynamics. This pharmacological profile makes ketamine an attractive sedative, potentially reducing the necessity for other sedatives and vasopressors, but there are no studies evaluating its effect on these medications in patients requiring deep sedation for acute respiratory distress syndrome.
*Materials and methods:* This is a retrospective, observational study in a single center, quaternary care hospital in southeast Texas. We looked at adults with COVID-19 requiring mechanical ventilation from March 2020 to September 2020.
*Results:* We found that patients had less propofol requirements at 72 h after ketamine initiation when compared to 24 h (median 34.2 vs 54.7 mg/kg, p = 0.003). Norepinephrine equivalents were also significantly lower at 48 h than 24 h after ketamine initiation (median 38 vs 62.8 mcg/kg, p = 0.028). There was an increase in hydromorphone infusion rates at all three time points after ketamine was introduced.
*Conclusions:* In this cohort of patients with COVID-19 ARDS who required mechanical ventilation receiving ketamine we found propofol sparing effects and vasopressor requirements were reduced, while opioid infusions were not.

## 1. Introduction

Deep sedation and in severe cases neuromuscular blockade, may be required in the treatment of patients with acute respiratory distress syndrome (ARDS). This is done with the intent to reduce oxygen requirements of involuntary muscle movement, promote ventilator synchrony of lung protective strategies and improve tolerance to prone positioning during invasive mechanical ventilation [1].

Sedation and analgesia are critical components of the intensive care unit (ICU) practice, driving many clinical outcomes, especially when it involves the care of patients requiring mechanical ventilation [2].

Achieving adequate analgesia prior to sedation has been shown to reduce time of mechanical ventilation which is typically achieved by the use of opioids [3–5]. Although opioids are effective analgesics, their use has been associated with respiratory depression and constipation which can have detrimental effects on ventilator liberation [6]. Sedation is often obtained with non-benzodiazepine drugs, such as propofol and dexmedetomidine, as well as adjunctive benzodiazepines [1]. Propofol and dexmedetomidine, the latter which will not achieve deep sedation, may be associated with less than favorable effects on hemodynamic parameters such as hypotension and bradycardia. Furthermore, benzodiazepines can lead to increased rates of delirium which in turn can lead

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to prolonged mechanical ventilation, ICU length of stay and increased mortality [7].

Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, is often utilized as a sedative and non-opioid analgesic outside of ICU because its use is not associated with respiratory depression and maintains upper airway reflexes [8]. In addition, compared to other commonly utilized sedatives in the ICU, it does not cause hypotension or bradycardia and can be used as an adjunct agent in patients with severe bronchospasm since it induces smooth muscle relaxation of the lower airways [9,10]. These effects, coupled with its abilities to provide sedation, analgesia and amnesia, support ketamine's use as an adjunctive sedative for mechanically ventilated ICU patients.

High doses of opioids, benzodiazepine and non-benzodiazepine sedatives which are regularly utilized for deep sedation may expose patients to noxious side effects. Ketamine's therapeutic and safety effect profile make it an attractive choice as an adjunct sedative in patients with ARDS. However, there is scant data of how its addition can impact other sedatives and analgesics being used. We sought to describe the impact of continuous ketamine infusion on the requirements of other continuously infused sedatives, analgesics, paralytics and vasopressors in patients with COVID ARDS.

## 2. Materials and Methods

### 2.1. Study design and participants

We performed a retrospective, observational chart review of patients with ARDS secondary to COVID-19 admitted to the intensive care unit at Baylor-St. Luke's Medical Center, an 800-bed quaternary care referral hospital, from March 1st, 2020 to September 15, 2020. Patients were identified through the electronic medical record by using Cogito SlicerDicer (Epic 2018, Verona, WI). We included patients who were 18 years of age and older with a positive SARS-CoV2 PCR, required invasive mechanical ventilation for ARDS, as stated in the chart, for greater than 24 h, and had ketamine infusion started. Patients who were pregnant or were admitted to the hospital for a surgical procedure were excluded.

The study was performed in accordance with Baylor College of Medicine's and Baylor-St. Luke's Medical Center institutional review board requirements, approval number H-48533.

### 2.2. Data collection

Data collected included patient demographics including age, sex, race, ethnicity, and co-morbidities. APACHE II score was calculated at the time of ICU admission. We also collected detailed data regarding rates of sedatives, analgesics, paralytics and vasopressors utilized for each patient. The cumulative doses of each sedative, opioid, non-depolarizing muscle relaxants, and vasopressor were calculated for 24-h periods, including the 24 h prior to the start of the ketamine infusion, 24 h post, 24–48 h post and 48–72 h post-initiation of ketamine. The cumulative doses were calculated based on the documented rates of each infusion. The dose of each vasopressor was converted to norepinephrine equivalents in order to comparatively assess vasopressor use.

### 2.3. Statistical analysis

Patient baseline characteristics were summarized by median with minimum and maximum values, or frequency with percentage. Friedman's chi-square test was used to compare sedative, opiate, non-depolarizing muscle relaxants and vasopressor dosages between time points. If significant, pairwise Friedman tests were conducted between each time point, and p-values were adjusted for multiple comparisons using Holm's method. P-values $< 0.05$ were considered statistically significant. Analyses were performed utilizing Stata 16 (StataCorp LLC, College Station, TX).

## 3. Results

### 3.1. Demographics

We identified 59 patients receiving ketamine, their demographics and patient characteristics are shown in Table 1. Ketamine dose did not significantly change over time after its initiation ($p = 0.184$) (Fig. 1).

### 3.2. Use of sedatives

#### 3.2.1. Propofol
A total of 51 patients received propofol and ketamine concomitantly. Median total propofol dose was significantly different on at least two time points ($p = 0.005$) after ketamine initiation. The median total dose of propofol was significantly lower at 72 h compared to the initial 24 h after ketamine initiation (median 34.2 vs 54.7 mg/kg, $p = 0.003$).

#### 3.2.2. Midazolam
Out of the 21 patients who received midazolam and ketamine, there was no significant change of midazolam dosing over time ($p = 0.763$).

#### 3.2.3. Dexmedetomidine
A total of 26 patients received dexmedetomidine and ketamine without a significant change of dexmedetomidine dosing ($p = 0.764$).

#### 3.2.4. Opioid analgesics
Fentanyl and ketamine were both given to 11 patients and there was not a significant change in fentanyl dosing ($p = 0.136$) between time points, as opposed to the 47 patients who received ketamine and hydromorphone who had an increase in the dosage of analgesic after

**Table 1**
Patient characteristics.

| Variable | Median (Min-Max) n = 59 |
|---|---|
| Age at ICU admission | 58.4 (29–86) |
| BMI | 34.2 (19–52) |
| APACHE II Score | 14 (3–28) |

| Variable | |
|---|---|
| Race/Ethnicity, n (%) (n = 56) | |
| Non-Hispanic White | 14 (25) |
| Hispanic | 29 (51) |
| Black or African American | 11 (20) |
| Other | 2 (4) |
| Obesity (BMI ≥30), n | |
| No | 15 |
| Yes | 44 |
| | |
| Age at ICU Admission, n (%) | |
| ≤44 | 7 (12) |
| 45-54 | 19 (32) |
| 55-64 | 16 (27) |
| 65-74 | 14 (24) |
| >74 | 3 (5) |
| | |
| Comorbidity, n (%) | |
| Chronic Kidney Disease | 5 (9) |
| ESRD | 6 (10) |
| Hypertension | 43 (73) |
| Diabetes | 34 (58) |
| Congestive Heart Failure | 7 (12) |
| Chronic Liver Disease | 1 (2) |
| COPD | 5 (9) |
| Asthma | 4 (7) |
| Atrial Fibrillation | 2 (3) |
| | |
| Source of ICU Admit, n (%) | |
| Outside Hospital Transfer | 31 (53) |
| Emergency Center | 24 (41) |
| Acute Care Floor | 4 (7) |
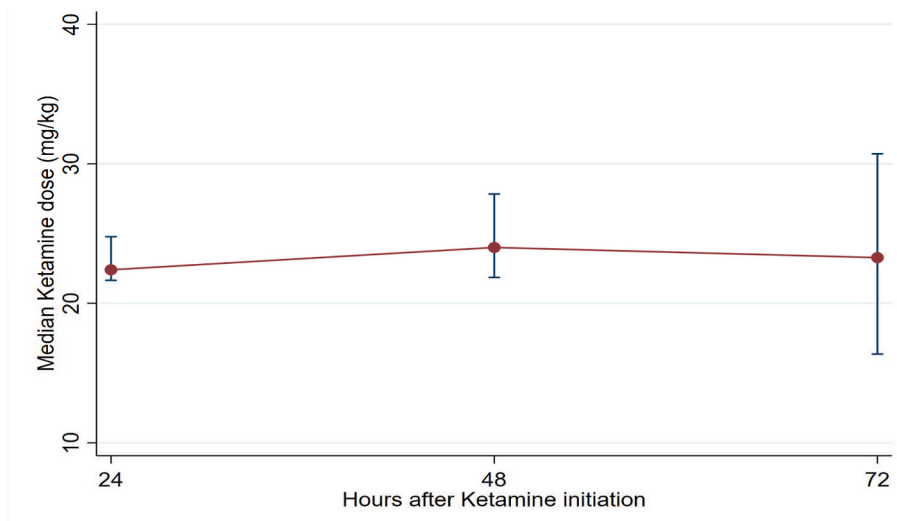
**Fig. 1. Ketamine dose over time** Median cumulative dosage of ketamine infused to patients over time for each 24-h period after initiation.

ketamine was introduced (p=<0.001). Compared to pre-ketamine initiation, median hydromorphone dose was higher at 24 h (median 36.1 vs 18.8 mg, p < 0.001), 48 h (median 36 vs 18.8 mg, p = 0.007), and 72 h (median 38.9 vs 18.8 mg, p = 0.014).

### 3.2.5. Non-depolarizing muscle relaxants

Cisatracurium was used in 32 patients and its dose was increased significantly 72 h after ketamine was introduced compared to before ketamine (median 1.9 vs 0.2 mg/kg, p = 0.009). Rocuronium was used in 8 patients. Total rocuronium dose was significantly different between at least 2 time points (p = 0.015). However, when performing pairwise comparisons, and adjusting p-values for multiple comparisons, rocuronium dose was not significantly different between any time points.

### 3.2.6. Norepinephrine

A total of 50 patients required vasopressor support during the analyzed time-frame. Agents include norepinephrine and vasopressin, which were converted to norepinephrine equivalents (Fig. 2). The dose
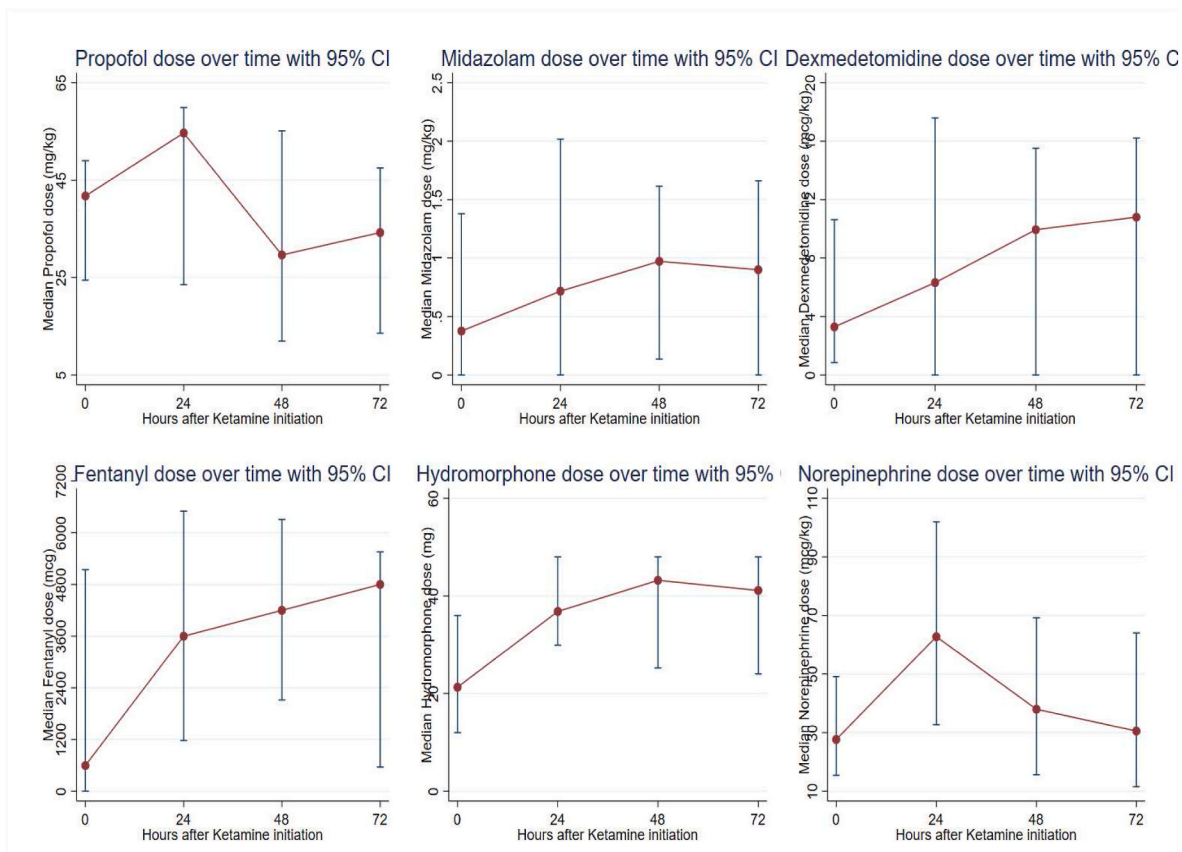


**Fig. 2. Median Doses of Infusions Over Time** Median cumulative dose of infusions during each 24-h period before and after ketamine initiation. **A,** propofol; **B,** midazolam: **C,** dexmedetomidine; **D,** fentanyl; **E,** hydromorphone; **F,** norepinephrine.

of norepinephrine equivalents significantly declined 48 h after ketamine was introduced compared to the first 24 h it was introduced (median 38 vs 62.8 mcg/kg, p = 0.028). There was also a nonsignificant decline in norepinephrine 72 h after ketamine was introduced compared to first 24 h (median 30.53 vs 62.8 mcg/kg, p = 0.055).

## 4. Discussion

To our knowledge this is the only published study looking at the impact of ketamine on other sedative, analgesic, paralytic and vasopressor infusions in patients requiring sedation for ARDS. In this retrospective, observational cohort of COVID-19 ARDS ICU patients on mechanical ventilation requiring sedation, we found that the introduction of a ketamine infusion decreased propofol and norepinephrine requirements (Fig. 2). The propofol sparing effects of ketamine have previously been described in other studies targeting light sedation, but none have evaluated its use in targeted deep sedation [11]. This is important because continuous infusions of propofol at high doses and for a prolonged time can increase the risk for propofol related infusion syndrome, hypertriglyceridemia and pancreatitis [12,13]. ARDS patients who require deep sedation are especially at risk for complications related to propofol [14]. A vasopressor sparing effect was also noted in our cohort of patients. A significant reduction at 48 h compared to 24 h was seen, with a nonsignificant reduction at 72 h after ketamine was introduced. This is consistent with what has been reported in the literature when ketamine is used for light sedation in mechanically ventilated patients [15]. Given the retrospective design we cannot reliably determine the etiology for hypotension indicating vasopressors, but with 86% of our patients being on propofol it could be a major contributing factor.

With regards to opioids, we did not observe any changes in median fentanyl requirements, however, did observe an increase in median hydromorphone requirements. Our findings are similar to those of Perbet et al. in which ketamine did not have an impact on the amount of opioids being infused, and are at contrast with different reports of ketamine having opiate sparing effects [16,17]. This could be explained if opioids were titrated to sedation goals instead of analgesic goals. Notably, we excluded any surgical patients, who may have required higher analgesic doses. In addition, the majority of our patients were referred from outside facilities, therefore, opioid use prior to their arrival to our facility is unclear. We had a high obesity population in our cohort, which may have contributed to higher requirements of opioids and attenuated the impacted of ketamine. Of note, our institution favored hydromorphone infusions over fentanyl due in part to drug supply shortages during the time period this cohort of patients was studied.

Ketamine did not have any significant impact on benzodiazepines or paralytics when these were being used. Although neutral effects on benzodiazepine infusions have been reported, we did not find any reports on the effects of paralytics [18]. We would have assumed there would be some benzodiazepine sparing effect by adjunctively using ketamine, as seen with propofol, but this was not detected in our population. It may be presumed that ketamine was added with the intention to reduce propofol dosing rather preferentially to benzodiazepines infusions, which might be the reason no effect on benzodiazepine dosing was seen in this cohort. The high number of patients on propofol (51 out of 59) and vasopressors (50 out of 59) within this cohort could support this goal of reducing propofol and possibly vasopressors as the indication for ketamine being initiated for many of these patients.

A minority of patients had concomitant ketamine and dexmedetomidine infusion (n = 26). We did not observe an impact on the median amount of dexmedetomidine dose after ketamine was started. Dexmedetomidine will not achieve deep sedation on its own, therefore we did not expect any changes to its dosing after ketamine initiation. It is unclear why patients were on dexmedetomidine for deep sedation, but many patients came from outside facilities, and it might have been

started prior to the arrival to our facility with changes in its titration not being captured in the time frame patients were studied.

Limitations of this study include the retrospective nature, that not every patient received all of the drugs studied (e.g., midazolam, dexmedetomidine, rocuronium and fentanyl) and the fact that most of our patients came from other centers, therefore we are unaware what sedation dosages and practices were utilized before arriving to our center. Patients coming from an outside hospital could have been exposed to higher doses of opioids and benzodiazepines, building tolerance to them, thus requiring higher dosing, and dampening the effects of ketamine. In addition, we chose to look only at the initial 72-h after initiation of ketamine. This period was selected to detect the initial effect of ketamine on the other studied medications after its initiation. Another limitation is that we are not privy to the way sedation strategies were implemented. It seems ketamine was introduced to avoid escalation in other sedating agents, such as propofol or benzodiazepines, but was also combined with opioids to continue the same level of sedation.

The findings of propofol and vasopressor infusion reductions after initiating ketamine are less surprising in this retrospective setting as the reduced hypotension associated with ketamine use was likely a factor in selecting ketamine as a sedative in these patients [19].

## 5. Conclusion

Ketamine remains an attractive option in patients with COVID-19 ARDS that require mechanical ventilation and deep sedation. We did find a propofol and vasopressor sparing effect after starting ketamine. Findings included a significant reduction in median propofol dose at 72 h and a significant reduction in median vasopressor dosing at 48 h compared to the 24 h period after starting ketamine, with other time periods also trending toward reduction. This propofol and vasopressor sparing effect may lead to fewer complications related to the infusion of these medications. In contrast to prior studies we found an increase use of hydromorphone, the most common opiate used in this study, after ketamine was started. Further prospective studies are needed to assess the efficacy and clinical benefits of ketamine as a sedative in mechanically ventilated ARDS patients.

### CRediT authorship contribution statement

**Orlando Garner:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Resources, Data curation. **Jonathan Patterson:** Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Investigation, Writing – review & editing. **Julieta Muñoz Mejia:** Investigation. **Vijay Anand:** Investigation. **Juan Deleija:** Investigation. **Christopher Nemeh:** Investigation. **Meghna Vallabh:** Investigation, Methodology, Writing – review & editing. **Kristen A. Staggers:** Formal analysis, Data curation, Methodology. **Christopher M. Howard:** Investigation, Writing – review & editing. **Sergio Enrique Treviño:** Investigation, Writing – review & editing. **Muhammad Asim Siddique:** Investigation, Resources, Writing – review & editing. **Christopher K. Morgan:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration.

### Declaration of competing interest

The authors have no conflict of interests to declare with regards to this submission.

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