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Continuous infusion of ketamine for adjunctive analgosedation in mechanically ventilated patients with chronic obstructive pulmonary disease

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Abstract:

BACKGROUND AND AIM: Ketamine is a fast-acting, hypnotic, amnestic agent that may be used to manage pain and agitation which is refractory to commonly used sedatives and analgesics. However, there is a paucity of literature describing the effects of continuous infusion of ketamine on sedative and analgesic consumption and delirium in mechanically ventilated patients. This investigation describes a single institution's use of ketamine infusions as a part of a sedation protocol in the respiratory intensive care unit (RICU).

METHODS: This was a retrospective cohort study of mechanically ventilated patients with chronic obstructive pulmonary disease (COPD) who received ketamine infusions as a part of a sedation protocol in a 16-bed RICU. The patients have assessed sedative consumption, analgesic consumption, and delirium incidence.

RESULTS: A total of 100 COPD patients receiving ketamine continuous infusion as a part of a sedation protocol between November 2017 and April 2020 were eligible and enrolled in this study. We found that patients had a reduction in opioid and benzodiazepine requirements at 24, 48, and 72 h after ketamine initiation ($p<0.05$). In addition, significant reductions in vasopressor requirements were observed at 24, 48, and 72 h after ketamine initiation ($p<0.05$). During the analyzed time frame, all patients received ketamine infusion at 4 μg/kg/min. There were no reported adverse drug reactions.

CONCLUSIONS: In this cohort of COPD patients who required mechanical ventilation we found decreased benzodiazepine, opiate, and vasopressor doses when the addition of a ketamine infusion, with no adverse drug reactions. Further prospective research is warranted to define optimal dosing strategies.

Keywords:

COPD, ketamine, mechanical ventilation, sedation

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Introduction

The appropriate sedation and analgesia of mechanically ventilated patients to manage their anxiety, decrease excessive oxygen consumption, and facilitate care can be challenging. Although commonly used sedatives and analgesics are effective for many patients, they are associated with numerous side effects including opioid-induced constipation and hemodynamic instability associated with propofol and dexmedetomidine.[1,2] Furthermore, the administration of opiates alone or in combination with benzodiazepines has been identified as a risk factor for delirium, which involves changes in consciousness, attention, cognition, and perception.[3,4]

Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, provides sedation, amnesia, and analgesia and also maintains pulmonary compliance while reducing airway resistance.[5–7] Therefore, ketamine offers an additional option for sedation in mechanically ventilated patients with chronic obstructive pulmonary disease (COPD).

The pharmacological profile of ketamine makes it an appealing sedative, but literature evaluating its effect on traditional agents (e.g., fentanyl and midazolam) in mechanically ventilated patients is limited. In this study, we postulated that continuous infusion of ketamine may decrease sedative and analgesic consumption and also delirium incidence in mechanically ventilated patients with COPD.

Materials and Methods

Study design and settings

This is a single-center observational retrospective study in our 16-bed respiratory intensive care unit (RICU) which receives about 600–650 inpatients/year. The study protocol was reviewed and approved by the local Institutional Ethical Board (approval number 2021-134 and date July 1, 2021). This study was carried out in accordance with the Helsinki Declaration.

Our unit follows an institutional physician-driven protocol based on targeting the sedation status to Richmond Agitation Sedation Scale scores of −2 to +1.[8] The protocol includes a first line sedation strategy using a continuous infusion of either an opioid (fentanyl, starting dose 0.7 μg/kg/h), a benzodiazepine (midazolam, starting dose 0.03 mg/kg/h), or more frequently, a combination of both, based on patients' clinical characteristics and their expected trajectory of illness. In the case of suboptimal analgosedation despite the use of high dosages of opioids and benzodiazepines, a second line analgosedation agent received a continuous infusion of ketamine at the dose of 4 μg/kg/min. The onset of delirium was monitored each day using the confusion assessment method for the ICU (CAM-ICU) by bedside nurses.[9]

Study population

We included all mechanically ventilated patients with COPD who received ketamine infusions for 24 h or longer between November 2017 and April 2020. Patients who were pregnant or in lactation, who had psychosis as defined by the Diagnostic and Statistical Manual of Mental Disorders-IV, who received concomitant neuromuscular blockers, who showed chronic use of opiates, and who started on ketamine on day 1 of mechanical ventilation were excluded from the study.

Data collection

All data from this study were obtained by retrospective querying of the institutional electronic system and medical charts. The following variables were collected: (1) demographic characteristics, age, sex, and weight; (2) clinical baseline features including comorbidities, the Acute Physiologic and Chronic Health Evaluation (APACHE) II score, the Sequential Organ Failure Assessment (SOFA) score; (3) characteristics of ICU stay, including length of MV, length of ICU stay, 28-day mortality, and 90-day mortality; (4) type and dosages of concomitant continuous infusions of analgesics, sedative, and vasopressor drugs in 72 h before and after initiation of ketamine infusion; (5) cases of withdrawal syndrome and delirium throughout ICU stay; and (6) all adverse events (AEs) with onset during the ketamine infusion.

Outcome measures

For our study, when used as an adjuvant for difficult sedation, ketamine was considered effective if no increases in the dosages of other analgesics and sedatives had been necessary within the 72 h of ketamine infusion. Finally, the ketamine safety profile was evaluated as a secondary endpoint, with particular attention to hypertension, tachycardia, laryngospasm, hypersalivation, emesis, nystagmus, anaphylaxis, and erythema.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences for Windows version 26.0 software package (SPSS, Chicago, IL, USA). Normality of distribution was assessed using the Shapiro–Wilk test. Quantitative variables have been expressed as mean±standard deviation and median [Interquartile Range]. The hemodynamic properties, sedative usage, analgesic usage, and vasopressor usage between pre- and post-ketamine infusion were assessed by the Wilcoxon signed-rank test. P<0.05 was considered statistically significant.

Results

During the evaluation period, we identified 135 mechanically ventilated COPD patients who met the inclusion criteria. Twenty-eight patients were excluded for concomitant neuromuscular blocker therapy, 5 patients were excluded for receiving ketamine infusion for less than 24 h, and 2 patients did not have complete documentation. Of the 100 patients included in the analysis, the majority of patients were male, with 65.1±13.4 years (Table 1).

Adjunctive analgesics and sedatives were reduced without the initiation of alternative sedatives. Daily consumption of fentanyl was significantly reduced 24 h [2.25±1.56 vs 1.71±1.56 μg/kg/h (p<0.001)], 48 h [2.25±1.56 vs 1.20±1.62 μg/kg/h (p<0.001)], and 72 h [2.25±1.56 vs 0.52±1.11 μg/kg/h (p<0.001)] after ketamine was introduced (Table 2). Compared with pre-ketamine initiation, the midazolam dose also was lower at 24 h [0.21±0.71 vs 0.14±0.59 mg/kg/h (p=0.007)], 48 h [0.21±0.71 vs 0.10±0.47 mg/kg/h (p<0.001)], and 72 h [0.21±0.71 vs 0.13±0.58 mg/kg/h (p<0.001)] (Table 2).

Hemodynamic parameters of the patients are presented in Table 2. During the analyzed time frame, heart rate and blood pressure did not change significantly. Sixty-five patients in our cohort needs vasopressor support, 19 patients continued on the vasopressor support, and 46 had vasopressors discontinued. The dose of norepinephrine was significantly reduced after ketamine initiation at 24 h [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)], and 72 h [0.12±0.18 vs 0.06±0.2 μg/kg/min (p<0.001)] (Table 3).

During the analyzed time frame, all patients received ketamine infusion at 4 μg/kg/min. The incidence of an AE in our patient population possibly attributed to ketamine was also reviewed. There were no reported AEs. Also, none of the patients developed hypersalivation requiring the use of atropine.

Table 1: Baseline characteristics and treatment outcomes of patients

Variable	All patients (n=100)	
	n	%
Age (years)	65.1±13.4	
Male	74	74
Body mass index		
Underweight	3	3
Normal	44	44
Overweight	35	35
Obese	17	17
Morbid obese	1	1
Comorbidities		
Hypertension	35	35
Diabetes	14	14
CHF	30	30
CKD	12	12
APACHE II score	26.3±7.6	
SOFA score at ICU admission	7.2±2.9	
Creat Cl (mL/min)	79.6±35.9	
Vasopressor used	34	34
Mechanical ventilation length, median [IQR] (days)	11 [6–18]	
ICU length of stay	18.6±12.8	
Delirium status	12	12
28-day mortality	38	38
90-day mortality	41	41

Data presented as mean±standard deviation unless otherwise indicated. Body mass index is classified as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (30–39.9 kg/m^2), and morbid obese (>40 kg/m^2). CHF: Congestive heart failure, CKD: Chronic kidney diseases, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, ICU: Intensive care unit, Creat Cl: Creatinine clearance, IQR: Interquartile range

Delirium in ICU is associated with diagnostic challenges because the patient was unable to participate in the CAM-ICU evaluation. Twelve (12%) patients tested positive for delirium during their ICU stay.

Discussion

In this study, patients received significantly lower doses of benzodiazepine, opiate, and vasopressor dose when ketamine was initiated as a part of a multidrug sedation regimen, with no adverse reactions. To our knowledge, this is the first study to show the benefits of low-dose ketamine infusion in mechanically ventilated COPD patients.

Table 2: Continuous infusion analgesic and sedative dose requirements before and after ketamine initiation

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)		4	4	4
Fentanyl, n	100	77	51	27
Dose (μg/kg/h)	2.25±1.56	1.71±1.56*	1.20±1.62*	0.52±1.11*
Midazolam, n	100	60	44	26
Dose (mg/kg/h)	0.21±0.71	0.14±0.59*	0.10±0.47*	0.13±0.58*

Data presented as mean±standard deviation unless otherwise indicated. n represents the number of patients on continuous infusion. *P<0.05 as a comparison of dosing at each specified time point to the original dosing at the time of ketamine initiation

Table 3: Comparison of hemodynamic parameters and vasopressor medications during the analyzed time frame

Hemodynamic parameters and medications	Pre-ketamine	24 h after ketamine initiation	48 h after ketamine initiation	72 h after ketamine initiation
SBP (mmHg)	112±18.84	116.00±21.63	106.48±41.86	90.85±58.05
DBP (mmHg)	58.15±11.7	59.61±13.78	52.57±21.06	50.56±28.44
HR (beats/min)	91.76±24.49	86.09±15.63	79±35.53	68±44.03
Noradrenaline, n	65	60	34	19
Dose (mg/kg/min)	0.12±0.18	0.09±0.14*	0.06±0.17*	0.06±0.2*

Data presented as mean ± standard deviation unless otherwise indicated. n represents the number of patients on continuous infusion. *P<0.05 as a comparison of dosing at each specified time point to the original dosing at the time of ketamine initiation. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate

Achieving and maintaining adequate analgesia before sedation has been shown to decrease the duration of mechanical ventilation which is typically achieved by the use of opioids. The opioid-sparing effect of ketamine was observed in our cohort patients. Our finding is consistent with previous works of literature examining low-dose ketamine.[10–13] Ketamine is an agonist of the μ-, δ-, κ-opioid receptors and an antagonist of NMDA, which may explain the reduction in opioid consumption.[14,15]

Our study demonstrated that the use of ketamine infusion in mechanically ventilated patients reduced not only opioid consumption but also the use of benzodiazepine without compromising adequate sedation. The benzodiazepine sparing effects of ketamine are consistent with the existing literature targeting light sedation strategy despite that none have evaluated its use in describing deep sedation.[16,17] This is important because continuous infusions of benzodiazepines for a prolonged time are related to delirium, long-term cognitive dysfunction, and a longer duration of mechanical ventilation.[18,19]

In addition to its favorable respiratory dynamics profile, ketamine may have a chronotropic effect on the cardiovascular system, mediated by the sympathetic nervous system.[14] We observed a significant reduction in vasopressor requirement in our cohort of patients. This is consistent with what has been reported in the literature when low-dose ketamine is used for light sedation in mechanically ventilated adult patients.[11]

Delirium in critically ill patients is important as it is associated with diagnostic challenges and therapeutic dilemmas, and each additional day of delirium is associated with a 10% increased risk of death.[20,21] Currently, dexmedetomidine appears to show promising results, but it is an expensive molecule that may be associated with numerous side effects like bradycardia, hypotension, hypertension, nausea, and atrial fibrillation.[22,23] Also, several studies suggest that due to immune-regulatory properties in the peripheral and central nervous system, ketamine can be used for the treatment of delirium and depression.[24,25] Using the CAM-ICU, 12 patients (12%) were tested positive for delirium during their ICU stay. This was much lower than expected, as the incidence of delirium in mechanically ventilated patients admitted to the RICU had been reported to be as high as 24.4%.

Recent studies have suggested that ketamine has been associated with both the proconvulsant and anticonvulsant effects.[26] In this study, the seizure was not observed in any patients receiving ketamine. Additionally, ketamine

use has been associated with hypersalivation which is often managed with glycopyrrolate or atropine.[27] None of the patients received pharmacotherapy because of hypersalivation. Some studies noted potential adverse effects including hypertension and tachyarrhythmias, which were not noted in any of the patients while on ketamine. Ketamine infusion at lower doses (<10 μg/kg/min) does not seem to induce the psychomimetic side effects observed at higher doses.[11]

Our study has some limitations. The study was a single-center study and had a retrospective design, inability to manage interventions to influence analgesic and sedative requirements.

Conclusion

Despite these limitations, the current study highlights a favorable safety profile of low-dose ketamine without significant effects on hemodynamics or agitation. The initiation of ketamine infusion was associated with a significant decrease in overall fentanyl and midazolam requirements, suggesting a reasonable alternative for analgosedation in mechanically ventilated patients. However, prospective studies are needed to confirm these results and to determine the ideal dosing of ketamine in this setting.

Conflicts of interest
There are no conflicts of interest.

Ethics Committee Approval
The study was approved by the Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Clinical Research Ethics Committee (No: 2021-134, Date: 01/07/2021).

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Externally peer-reviewed.

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Concept – M.H., M.T.; Design – M.H., B.İ.F., A.K.; Supervision – M.H.; Funding – M.H.; Materials – None; Data collection &/or processing – B.İ.F., A.K.; Analysis and/or interpretation – M.H., B.İ.F., A.K., M.T.; Literature search – M.H., B.İ.F.; Writing – M.H., B.İ.F., A.K., M.T.; Critical review – M.H., M.T.

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