Saudi Pharmaceutical Journal 32 (2024) 102061

HOSTED BY

ELSEVIER

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Ketamine-based Sedation Use in Mechanically Ventilated Critically Ill Patients with COVID-19: A Multicenter Cohort Study

Ohoud Aljuhani [a], Khalid Al Sulaiman [b,c,d,e,m,*], Ghazwa B. Korayem [f], Ali F. Altebainawi [g,n], Abdulrahman Alshaya [b,c,d], Majed Nahari [h], Khuzama Alsamnan [f], Munirah A. Alkathiri [b], Bodoor S. Al-Dosari [i], Abeer A. Alenazi [j], Samiah Alsohimi [j], Lina I. Alnajjar [f], Mashael Alfaifi [b], Nora AlQussair [b], Reem M. Alanazi [c], Munirah F. Alhmoud [c], Nadin L. Alanazi [b], Hadeel Alkofide [k], Aljawharah M. Alenezi [c], Ramesh Vishwakarma [l]

[a] Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia
[b] Pharmaceutical Care Department, King Abdulaziz Medical City, Riyadh, Saudi Arabia
[c] College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[d] King Abdullah International Medical Research Center-King Saud Bin Abdulaziz University for Health Sciences, Ministry of National Guard – Health Affairs, Riyadh, Saudi Arabia
[e] Saudi Critical Care Pharmacy Research (SCAPE) Platform, Riyadh, Saudi Arabia
[f] Department of Pharmacy Practice, College of Pharmacy, Princess Nourah bint Abdulrahman University, P.O. Box 84428, Riyadh 11671, Saudi Arabia
[g] Pharmaceutical Care Services, King Salman Specialist Hospital, Hail Health Cluster, Hail, Saudi Arabia
[h] Pharmaceutical Care Services, King Abdullah bin Abdulaziz University Hospital, Riyadh, Saudi Arabia
[i] Pharmaceutical Care Services, King Abdulaziz University Hospital, Jeddah, Saudi Arabia
[j] Pharmaceutical Care Department, Prince Sultan Military Medical City, Riyadh, Saudi Arabia
[k] Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[l] Norwich Medical School, University of East Anglia, Norwich, United Kingdom
[m] Saudi Society for Multidisciplinary Research Development and Education (SCAPE Society), Riyadh, Saudi Arbia
[n] Department of Clinical Pharmacy, College of Pharmacy, University of Hail, Hail, Saudi Arabia

ARTICLE INFO

Keywords:
COVID-19
Ketamine
Oxygenation parameter
PaO2/FiO2 ratio
Length of Stay
Critically ill
Intensive care units (ICUs)
Lactic Acid
Mortality
SARS-CoV-2
Acute respiratory distress syndrome (ARDS)

ABSTRACT

Backgrounds: Ketamine possesses analgesia, anti-inflammation, anticonvulsant, and neuroprotection properties. However, the evidence that supports its use in mechanically ventilated critically ill patients with COVID-19 is insufficient. The study's goal was to assess ketamine's effectiveness and safety in critically ill, mechanically ventilated (MV) patients with COVID-19.

Methods: Adult critically ill patients with COVID-19 were included in a multicenter retrospective-prospective cohort study. Patients admitted between March 1, 2020, and July 31, 2021, to five ICUs in Saudi Arabia were included. Eligible patients who required MV within 24 hours of ICU admission were divided into two sub-cohort groups based on their use of ketamine (Control vs. Ketamine). The primary outcome was the length of stay (LOS) in the hospital. P/F ratio differences, lactic acid normalization, MV duration, and mortality were considered secondary outcomes. Propensity score (PS) matching was used (1:2 ratio) based on the selected criteria.

Results: In total, 1,130 patients met the eligibility criteria. Among these, 1036 patients (91.7 %) were in the control group, whereas 94 patients (8.3 %) received ketamine. The total number of patients after PS matching, was 264 patients, including 88 patients (33.3 %) who received ketamine. The ketamine group's LOS was significantly lower (beta coefficient (95 % CI): −0.26 (−0.45, −0.07), P = 0.008). Furthermore, the PaO2/FiO2 ratio significantly improved 24 hours after the start of ketamine treatment compared to the pre-treatment period (6 hours) (124.9 (92.1, 184.5) vs. 106 (73.1, 129.3; P = 0.002). Additionally, the ketamine group had a substantially shorter mean time for lactic acid normalization (beta coefficient (95 % CI): −1.55 (−2.42, −0.69), P 0.01). However, there were no significant differences in the duration of MV or mortality.

* Corresponding author at: King Abdulaziz Medical City (KAMC) - Ministry of National Guard Health Affairs (MNGHA), King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, PO Box 22490, 11426 Riyadh, Saudi Arabia.
E-mail address: alsulaimankh@ngha.med.sa (K. Al Sulaiman).

https://doi.org/10.1016/j.jsps.2024.102061
Received 2 September 2023; Accepted 1 April 2024
Available online 3 April 2024

Conclusions: Ketamine-based sedation was associated with lower hospital LOS and faster lactic acid normalization but no mortality benefits in critically ill patients with COVID-19. Thus, larger prospective studies are recommended to assess the safety and effectiveness of ketamine as a sedative in critically ill adult patients.

1. Introduction

Critically ill patients with COVID-19 admitted to the intensive care units (ICUs) have shown a heightened mortality rate, ranging from 26 % to 67 % (Arentz et al., 2020; Grasselli et al., 2020). These critically ill patients usually present with severe symptoms and acute respiratory distress syndrome (ARDS) (Grasselli et al., 2020; Guan et al., 2020). ARDS occurs in approximately 42 % of patients presenting with COVID-19, and it is the leading cause of mortality among those individuals (Hasan et al., 2020; Wu et al., 2020). Therefore, supportive therapies and mechanical ventilation (MV) are required for the management of ARDS (Fernando et al., 2021).

Sedatives and analgesics are essential components in the management of critically ill patients, especially in patients requiring MV (Kress and Hall, 2006). Benzodiazepines (BZD) or non-benzodiazepine sedatives, including propofol and dexmedetomidine, are commonly used agents (Bawazeer et al., 2020) However, the use of these agents is associated with several drawbacks (Breen et al., 2005; Faust et al., 2016). For instance, BZD may exacerbate delirium, resulting in prolonged MV, longer ICU stay, and higher mortality rate (Marra et al., 2017). Propofol may result in significant adverse reactions such as hypotension (26 %), bradycardia (1 % to 3 %), Hypertriglyceridemia (3 % to 10 %) and propofol-related infusion syndrome (1 %). (Kam and Cardone, 2007). Nonetheless, adequate analgesia preceding sedation has been associated with reduced ventilation duration, use of continuous infusion sedatives, and an overall lighter level of sedation (Breen et al., 2005; Faust et al., 2016). Thus, the use of sedative agents exhibiting analgesic properties, such as ketamine, may be preferred.

Ketamine is a short-acting anesthetic agent with analgesic and anti-inflammatory properties (Kurdi et al., 2014). It also has anticonvulsant activity and neuroprotective effects (Kurdi et al., 2014). Additionally, ketamine activates the sympathetic nervous system, leading to increased cardiac output, blood pressure, and heart rate. However, it preserves respiratory effort and airway reflexes by different mechanisms of action such as acting on various receptors in the lungs and inflammatory cascades, which induces bronchodilation and makes it a reasonable choice for patients with severe asthma who require MV (Chang et al., 2005; Hirota et al., 1996; Kolawole, 2001; Miller et al., 2011; Nehama et al., 1996; Pabelick et al., 1997; Sato et al., 1998; Zhu et al., 2007a; b). Ketamine can be safely administered with other sedatives as it reduces the hemodynamic instability caused by the co-administered sedatives (Garg et al., 2013; Uludağ et al., 2020). The combination of these benefits, along with its affordability, leads to a growing demand for its utilization in ICUs. (Groth et al., 2022; Umunna et al., 2015).

A single center retrospective study that assessed the impact of ketamine as an adjunct sedative in patients with respiratory failure due to COVID-19 pneumonia found that patients who received ketamine had reduced propofol and vasopressor requirements, whereas the need for opioid infusion was increased (Garner et al., 2021). In contrast, another retrospective observational study has demonstrated that the administration of ketamine is associated with higher hospital length of stay among mechanically ventilated patients with COVID-19 (Pata et al., 2021). Up to this point, the evidence that supports the use of ketamine in mechanically ventilated critically ill patients with COVID-19 is insufficient and uncertain. Therefore, the objective of this study is to evaluate the effectiveness and safety of ketamine among mechanically ventilated critically ill patients with COVID-19.

2. Methods

2.1. Study design

This study was carried out under the auspices of the Saudi Critical Care Pharmacy Research (SCAPE) platform, which also conducted other investigations to evaluate the safety and effectiveness of various therapies in critically ill patients (SCAPE, n.d.). The methodology of this multicenter cohort study is comparable to other studies executed by the SCAPE platform and previously reported (Al Harbi et al., 2022; Al Sulaiman et al., 2022a; b; Al Sulaiman et al., 2021a; b; Aljuhani et al., 2021). The supplemental material contains additional details on the study's design.

A retrospective-prospective cohort study was conducted across multiple centers, involving adult patients who were admitted to Intensive care units (ICUs) in five different locations in Saudi Arabia between March 1, 2020, and July 31, 2021, and had confirmed cases of COVID-19. The diagnosis of COVID-19 was confirmed using reverse transcriptase-polymerase chain reaction (RT-PCR) tests conducted on samples collected from either the nasopharynx or the throat. The enrolled patients were categorized into two groups based on whether they received intravenous ketamine during their ICU stay: the Control group (COVID-19 patients in the ICU who did not receive ketamine-based sedation) and the Ketamine group. Ketamine initiation was not based on predefined creteria at the included centers.

Throughout the patients' hospitalization, they were tracked until they were either discharged from the hospital or until their death while still undergoing treatment. The study was granted approval by the King Abdullah International Medical Research Center (KAIMRC) in June 2020 (Reference: RC20. 348.R). The research was carried out in compliance with the ethical guidelines outlined in the World Medical Association's Declaration of Helsinki for medical research involving human subjects (originally adopted in 1964 and revised in 2013) and pertinent national ethical regulations.

2.2. Study participants and settings

The details of included patients and the study settings are based on previously published studies of the same multicenter research group (30–32). We included adult patients (age $\geq$ 18 years) admitted to the ICUs with confirmed COVID-19. Patients were excluded if they did not require mechanical ventilation (MV) within 24 hours of ICU admission, had MV duration or ICU length of stay (LOS) $\leq$ one day, known history of pulmonary disease (e.g., Interstitial lung disease, bronchiectasis, pulmonary HTN), died within the first 24 hours of ICU admission or were labeled "Do-Not-Resuscitate" (Fig. 1). Details of study settings can be found in Supplementary File 1.

2.3. Data collection

The data for each participant was collected and managed using the Research Electronic Data Capture (REDCap®) software provided by the King Abdullah International Medical Research Center. The data collection was performed utilizing two components (retrospective and prospective). We gathered various information, including demographic data, comorbidities, vital signs, laboratory test results, baseline severity scores retrospectively. We recorded the details of ketamine initiation, such as the dose, duration, and timing, for eligible patients. Additionally, we have evaluated the study outcomes prospectively, such as LOS, ICU complications, and mortality. Further details for additional data

that are collected can be found in Supplementary File 1.

2.4. Outcomes

The primary outcome was the length of stay in the hospital. The secondary outcomes included improvements in oxygenation (PaO2/FiO2 ratio) and hemodynamic (HD) parameters up to six hours before initiation and the differences after 24 hours of Ketamine administration, time taken for lactic acid levels to normalize, 30 days and Hospital mortality rates, length of stay in the intensive care units (ICUs), duration of mechanical ventilation (MV), and occurrences of ICU-acquired complications such as new-onset atrial fibrillation, thrombosis, acute kidney injury (AKI), liver injury, hospital-acquired infection, and secondary fungal infection. (Supplementary File 1).

2.5. Statistical analysis

Ketamine-based sedation (Ketamine group) was matched in a 1:2 ratio with patients who did not receive it (control group) using the propensity score (PS) matching method (Proc PS match). These PS scores were calculated using propensity score analysis after taking into account all pertinent variables, including the patient's APACHE II score and proning status within 24 hours after ICU admission. Only patients whose PS logit differences between the two groups were 0.1 times or less than the combined estimate of the SD were considered to be matched. The propensity score, and the standardized mean difference (SMD) was used to examine the degree of PSM for prognostic variables included in the model. Less than 0.1 was considered an acceptable threshold. The detailed propensity score matching results are included in the appendix. Among all the pairings available, the smallest difference within each pair was observed when one patient from the ketamine group was matched with two patients from the control group (who did not receive ketamine). SAS, Cary, NC, was used for all analysis. Supplementary File 1 contains further details of these analyses.

3. Results

In the study, a total of 1650 patients who had been admitted to the ICUs with confirmed COVID-19 were initially screened. Among them, a total of 1,130 patients meets the inclusion criteria. (Fig. 1). Among the patients studied, 94 individuals, constituting 8.3%, received ketamine treatment, while 1036 patients (91.7%) were designated to the control group. Following the propensity score matching at a 1:2 ratio, the final evaluation included a cohort of 264 patients, with 88 of them (33.3 %) have received ketamine. The median duration of ketamine administration was 3.0 (2.00, 7.00) days, and the median daily dose administered was 5 (4.98, 9.32) mcg/kg/min. Of the patients treated with ketamine, 31 (35.2 %) patients received the drug within the initial 72-hour period after ICU admission. Other sedatives used in ketamine group either concomitantly or alternatively were fentanyl (n = 76, 76.1 %), followed by propofol (n = 65, 73.9 %), midazolam (n = 50, 56.8 %) and dexmedetomidine (n = 20, 22.7 %). In the control group, other sedatives were fentanyl (n = 81, 46.0 %), followed by midazolam (n = 50, 28.4. %), propofol (n = 49, 27.8 %) and dexmedetomidine (n = 44, 25.0 %) (Table 1).

3.1. Demographic and clinical characteristics

Before propensity score (PS) matching, the majority of the patients were male (n = 662, 61 %) with a mean age of 62.6 (±14.81). The most common comorbidities observed were diabetes mellitus (n = 648, 57.3 %), hypertension (n = 634, 56.1 %), and dyslipidemia (n = 235, 20.8 %). Interestingly, patients who received ketamine had higher APACHE II scores, proning status, levels of alanine transaminase (ALT), serum creatinine, and blood urea nitrogen (BUN) within 24 hours of ICU admission. However, after PS matching based on predefined criteria, most demographic and baseline characteristics became similar between the two groups. (Table 1).

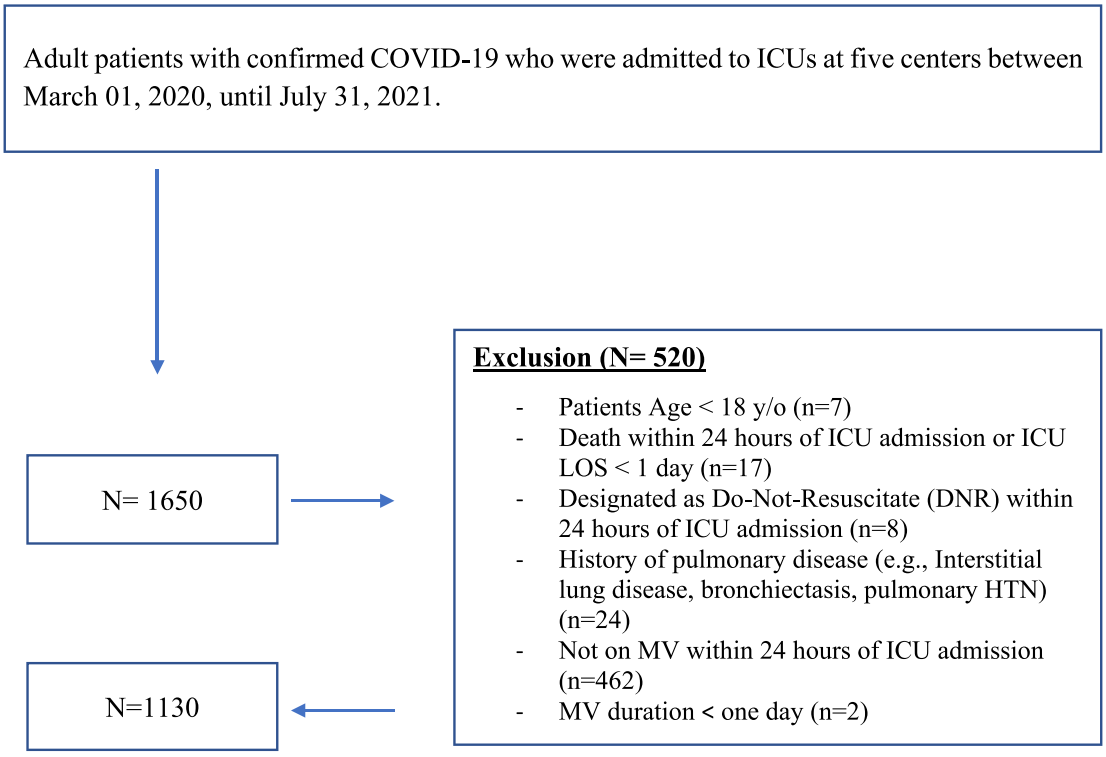

Fig. 1. Flowchart for eligibility criteria.

Table 1
Summary of Demography and Baseline characteristics.

	Before propensity score (PS)				After propensity score (PS)			
	Overall (N = 1130)	Control(N = 1036)	Ketamine Based(N = 94)	P-value	Overall (264)	Control(N = 176)	Ketamine Based(N = 88)	P-value
Age (Years), Mean (SD)	62.6 (14.81)	62.6 (14.88)	62.8 (14.02)	0.9040^	63.7 (14.20)	64.0 (14.25)	63.0 (14.16)	0.4901^
Gender – Male, n (%)	662 (61.0)	600 (60.4)	62 (68.1)	0.1458^^	168 (63.9)	107 (61.1)	61 (69.3)	0.1928^^
Weight (kg), Mean (SD)	81.6 (19.63)	81.6 (19.98)	81.5 (15.50)	0.5898^	83.8 (20.35)	84.8 (22.33)	81.6 (15.57)	0.4800^
APACHE II score, Median (Q1,Q3)	15.0 (11.00, 23.00)	15.0 (10.00, 22.00)	19.5 (12.00, 27.00)	0.0052^	19.0 (12.00, 26.00)	19.0 (12.00, 26.00)	19.5 (12.00, 27.00)	0.6520^
SOFA score, Median (Q1,Q3)	4.0 (2.00, 7.00)	4.0 (2.00, 7.00)	5.0 (3.00, 7.00)	0.1739^	6.0 (4.00, 8.00)	6.0 (4.00, 8.00)	6.0 (4.00, 8.50)	0.3486^
Early use of Dexamethasone within 24 h, n (%)	692 (61.2)	637 (61.5)	55 (58.5)	0.5707^^	155 (58.7)	102 (58.0)	53 (60.2)	0.7237^^
Early use of Methylprednisolone within 24 h, n (%)	116 (10.3)	105 (10.1)	11 (11.7)	0.6317^^	36 (13.6)	25 (14.2)	11 (12.5)	0.7036^^
Early use of Tocilizumab within 24 h, n (%)	231 (20.4)	216 (20.8)	15 (16.0)	0.2601^^	48 (18.2)	33 (18.8)	15 (17.0)	0.7350^^
Proning at admission, n (%)	258 (24.4)	229 (23.7)	29 (31.9)	0.0831^^	87 (33.0)	59 (33.5)	28 (31.8)	0.7812^^
Serum creatinine (mmol/L) at admission, Median (Q1,Q3)	91.0 (69.00, 137.50)	91.0 (69.00, 136.00)	92.0 (70.00, 151.00)	0.4802^	93.0 (70.00, 150.00)	94.0 (69.50, 147.50)	92.0 (70.00, 151.00)	0.8720^
Blood Urea nitrogen (BUN) at admission, Median (Q1,Q3)	7.4 (5.00, 12.80)	7.3 (5.00, 12.53)	8.1 (5.64, 15.10)	0.1584^	8.3 (5.40, 14.50)	8.5 (5.10, 14.36)	8.0 (5.64, 15.10)	0.8170^
Oxygenation Index (OI), Median (Q1, Q3)	16.7 (9.46, 26.77)	16.8 (9.54, 27.15)	15.5 (9.32, 25.15)	0.9177^	18.7 (10.15, 28.27)	20.7 (10.80, 28.41)	15.5 (9.32, 25.15)	0.3669^
Lactic acid Baseline, Median (Q1,Q3)	1.7 (1.29, 2.50)	1.7 (1.28, 2.50)	1.8 (1.30, 2.42)	0.9049^	1.8 (1.29, 2.44)	1.8 (1.28, 2.50)	1.7 (1.30, 2.40)	0.8925^
Platelets count Baseline, Median (Q1, Q3)	239.0 (184.00, 316.00)	239.0 (184.00, 317.00)	232.0 (187.00, 314.00)	0.9664^	244.0 (186.00, 317.00)	249.0 (184.00, 323.00)	234.0 (187.00, 314.00)	0.7409^
Total WBC Baseline, Median (Q1,Q3)	9.8 (6.64, 13.27)	9.8 (6.53, 13.24)	9.9 (7.42, 13.35)	0.1868^	9.9 (6.80, 14.25)	9.9 (6.24, 14.54)	9.8 (7.43, 13.68)	0.3374^
International normalized ratio (INR), Median (Q1,Q3)	1.1 (1.01, 1.20)	1.1 (1.00, 1.20)	1.1 (1.02, 1.18)	0.4944^	1.1 (1.02, 1.20)	1.1 (1.03, 1.20)	1.1 (1.02, 1.19)	0.9014^
activated partial thromboplastin time (aPTT) Baseline, Median (Q1,Q3)	30.3 (26.70, 34.00)	30.1 (26.60, 34.00)	31.5 (27.60, 34.00)	0.2316^	30.5 (27.00, 34.00)	30.0 (26.80, 34.00)	31.5 (27.60, 34.00)	0.2826^
Total bilirubin, Median (Q1,Q3)	9.2 (6.55, 14.00)	9.2 (6.60, 14.00)	8.9 (6.40, 14.00)	0.7553^	9.5 (6.30, 14.80)	9.7 (6.30, 15.00)	8.6 (6.40, 13.80)	0.4632^
Alanine transaminase (ALT) at admission, Median (Q1,Q3)	37.0 (24.00, 58.00)	36.0 (23.00, 57.00)	40.0 (27.00, 71.00)	0.0494^	37.0 (25.00, 60.00)	36.5 (24.00, 53.00)	39.0 (26.50, 67.00)	0.1617^
Aspartate transaminase (AST) at admission, Median (Q1,Q3)	51.0 (34.00, 77.00)	51.0 (34.00, 75.00)	52.0 (33.00, 102.00)	0.4398^	50.0 (35.00, 80.00)	51.0 (35.00, 71.00)	49.0 (32.00, 96.00)	0.6057^
Hematocrit at admission, Mean (SD)	0.4 (0.33, 0.42)	0.4 (0.33, 0.42)	0.4 (0.33, 0.43)	0.6088^	0.4 (0.33, 0.42)	0.4 (0.33, 0.42)	0.4 (0.33, 0.43)	0.5291^
Creatine phosphokinase (CPK) baseline (U/l), Median (Q1,Q3)	170.0 (72.00, 443.00)	169.5 (71.00, 448.00)	183.0 (87.00, 373.00)	0.5352^	170.0 (70.00, 424.00)	147.5 (59.00, 457.50)	183.0 (85.00, 373.00)	0.3526^
C-reactive protein (CRP) baseline (mg/l), Median (Q1,Q3)	133.8 (74.00, 203.00)	134.0 (74.00, 203.00)	133.3 (76.30, 205.00)	0.9292^	139.0 (76.80, 225.50)	145.0 (85.00, 233.00)	133.0 (76.00, 203.00)	0.4849^
Fibrinogen Level baseline (gm/l), Median (Q1,Q3)	5.4 (3.77, 7.18)	5.4 (3.82, 7.23)	5.5 (3.66, 6.60)	0.7410^	4.5 (2.85, 6.31)	4.4 (2.84, 6.06)	5.1 (2.96, 6.63)	0.7559^
D-dimer Level baseline, Median (Q1,Q3)	1.5 (0.72, 3.56)	1.5 (0.71, 3.56)	1.7 (0.83, 3.60)	0.3182^	1.5 (0.71, 3.70)	1.5 (0.69, 3.56)	1.7 (0.83, 3.90)	0.2712^
Ferritin Level baseline, Median (Q1,Q3)	679.0 (364.08, 1565.00)	688.9 (364.00, 1567.60)	567.8 (379.00, 1519.50)	0.5552^	676.9 (370.50, 1475.05)	723.9 (359.50, 1498.47)	555.9 (381.65, 1291.22)	0.6802^
Blood glucose level Baseline Within 24 h of ICU admission, Median (Q1,Q3)	11.0 (7.80, 15.90)	11.0 (7.80, 15.90)	11.4 (8.04, 15.30)	0.5824^	12.3 (8.60, 16.90)	13.0 (8.70, 17.10)	11.4 (8.08, 15.00)	0.2354^
Lowest PaO2/FiO2 ratio within 24 h of admission, Median (Q1,Q3)	80.9 (61.00, 125.00)	80.7 (61.18, 125.00)	90.9 (59.88, 125.00)	0.8368^	77.3 (57.70, 122.40)	74.4 (56.25, 117.80)	91.8 (59.88, 128.80)	0.1649^
Highest RASS at admission, Median (Q1, Q3)	−3.0 (−4.00, 0.00)	−3.0 (−4.00, 0.00)	−4.0 (−4.00, −2.00)	0.5460^	−4.0 (−4.00, −3.00)	−4.0 (−4.00, −3.00)	−4.0 (−4.00, −2.00)	0.8434^
Lowest RASS at admission, Median (Q1, Q3)	−3.0 (−4.00, −1.00)	−3.0 (−4.00, −1.00)	−3.5 (−4.00, −3.00)	0.4178^	−3.0 (−4.00, −3.00)	−3.0 (−4.00, −2.00)	−3.5 (−4.00, −3.00)	0.6679^
Respiratory rate (Breath Per Minute) at admission, Median (Q1,Q3)	28.0 (24.00, 33.00)	28.0 (24.00, 33.00)	27.0 (23.00, 33.00)	0.6078^	28.0 (24.00, 34.00)	29.0 (25.00, 34.00)	27.0 (23.00, 34.00)	0.2508^
Highest heart rate (HR) at admission, Median (Q1,Q3)	104.0 (92.00, 116.00)	103.0 (92.00, 116.00)	105.0 (90.00, 117.00)	0.7373^	106.0 (91.00, 119.00)	108.0 (92.00, 121.00)	105.0 (90.00, 116.00)	0.1403^
Lowest MAP at admission, Median (Q1, Q3)	71.0 (62.00, 81.00)	71.0 (62.00, 80.00)	72.0 (64.00, 83.00)	0.2557^	70.0 (61.00, 82.00)	70.0 (60.00, 80.00)	72.0 (64.00, 83.00)	0.0536^
Patient received nephrotoxic drugs/ material during ICU stay, n (%)*$	970 (89.6)	894 (89.9)	76 (86.4)	0.2912^^	230 (88.5)	157 (89.7)	73 (85.9)	0.3643^^
Comorbidity, n (%)								
Atrial fibrillation (A Fib)	47 (4.2)	43 (4.2)	4 (4.3)	0.9612**	13 (4.9)	9 (5.1)	4 (4.5)	0.8406**
Hypertension	634 (56.1)	580 (56.0)	54 (57.4)	0.7844^^	160 (60.6)	108 (61.4)	52 (59.1)	0.7216^^
Diabetes Mellitus	648 (57.3)	592 (57.1)	56 (59.6)	0.6481^^	164 (62.1)	109 (61.9)	55 (62.5)	0.9285^^
Dyslipidemia	235 (20.8)	220 (21.2)	15 (16.0)	0.2273^^	64 (24.2)	49 (27.8)	15 (17.0)	0.0537^^
Heart Failure	92 (8.1)	82 (7.9)	10 (10.6)	0.3553^^	27 (10.2)	17 (9.7)	10 (11.4)	0.6666^^

(*continued on next page*)

Table 1 (*continued*)

	Before propensity score (PS)				After propensity score (PS)			
	Overall (N = 1130)	Control(N = 1036)	Ketamine Based(N = 94)	P-value	Overall (264)	Control(N = 176)	Ketamine Based(N = 88)	P-value
Asthma	87 (7.7)	79 (7.6)	8 (8.5)	0.7579^^	20 (7.6)	12 (6.8)	8 (9.1)	0.5106^^
COPD	24 (2.1)	22 (2.1)	2 (2.1)	0.9979**	4 (1.5)	2 (1.1)	2 (2.3)	0.4761**
Ischemic heart disease (IHD)	100 (8.8)	94 (9.1)	6 (6.4)	0.3792^^	26 (9.8)	20 (11.4)	6 (6.8)	0.2426^^
Chronic kidney disease (CKD)	130 (11.5)	115 (11.1)	15 (16.0)	0.1576^^	37 (14.0)	23 (13.1)	14 (15.9)	0.5308^^
Cancer	56 (5.0)	52 (5.0)	4 (4.3)	0.7438**	16 (6.1)	12 (6.8)	4 (4.5)	0.4657^^
Deep Vein Thrombosis (DVT)	11 (1.0)	11 (1.1)	0 (0.0)	0.3154**	3 (1.1)	3 (1.7)	0 (0.0)	0.2180**
Pulmonary Embolism (PE)	11 (1.0)	11 (1.1)	0 (0.0)	0.3154**	3 (1.1)	3 (1.7)	0 (0.0)	0.2180**
Liver disease (any type)	26 (2.3)	26 (2.5)	0 (0.0)	0.1202**	3 (1.1)	3 (1.7)	0 (0.0)	0.2180**
Stroke	66 (5.8)	63 (6.1)	3 (3.2)	0.2527^^	11 (4.2)	8 (4.5)	3 (3.4)	0.6631**

*T Test /^Wilcoxon rank sum test is used to calculate the P-value.
^^Chi square/ ** Fisher's Exact test is used to calculate P-value.
*$ Nephrotoxic medications/ material included IV Vancomycin, Gentamicin, Amikacin, Contrast, Colistin, Furosemide, and/or Sulfamethoxazole/trimethoprim.
≠ Patients who received either Enoxaparin 40 mg daily or UFH 5000 Unit three times daily were grouped under the "standard dose VTE prophylaxis. Any patient who received higher than standard dose but not as treatment dose (Enoxaparin 1 mg/kg q12hr or 1.5 mg/kg q24hr or UFH infusion) was categorized as receiving "High VTE prophylaxis dose". On the other hand, lower VTE prophylaxis considered for patient who received Enoxaparin < 40 mg/day or Unfractionated heparin (UFH) < 5000 Units three times daily/day).

3.2. Length of stay and mechanical ventilation duration

The hospital length of stay (LOS) was significantly shorter in the ketamine group compared with the control (beta coefficient (95 % CI): −0.26 (−0.45, −0.07), p-value = 0.008). Furthermore, the ICU LOS was shorter in patients who received ketamine during ICU stay; however, it failed to reach the statistically significant (beta coefficient (95 % CI): −0.18 (−0.36, 0.00), p-value = 0.05). On the other hand, the median duration of mechanical ventilation (MV) was 11 days (5.0, 17.0) in patients who received ketamine, compared to 10 days in the control group. However, this difference was not statistically significant in both the crude analysis and regression analysis (beta coefficient (95 % CI): −0.16 (−0.38, 0.06), p-value 0.16) (Table 2).

Table 2
Clinical outcomes of critically ill patients with COVID-19 after PS matching.

Outcomes				beta coefficient (Estimates) (95 %CI)	P-value $*
	Control	Ketamine	P-value		
Hospital Length of Stay (Days), Median (Q1, Q3)	20.0 (12.00, 31.00)	17.0 (12.00, 27.00)	0.15^	−0.26 (−0.45,−0.07)	0.008
MV duration (Days), Median (Q1, Q3)	10.0 (5.00, 19.00)	11.0 (5.00, 17.00)	0.54^	−0.16 (−0.38,0.06)	0.16
ICU Length of Stay (Days), Median (Q1, Q3)	14.0 (8.00, 24.50)	12.0 (8.00, 18.50)	0.25^	−0.18 (−0.36,0.00)	0.05
Time for lactic acid normalization (Hours), Mean (SD)	22.8 (25.80)	4.9 (14.16)	<0.01^	−1.55 (−2.42,−0.69)	0.0004
				Hazard Ratio (HR) (95 %CI)	P-value $
30-day mortality, n (%)	84 (50.9)	46 (54.8)	0.57^^	1.24 (0.86, 1.78)	0.25
In-hospital mortality, n (%)	99 (59.3)	52 (59.8)	0.94^^	1.12 (0.87, 1.71)	0.25

*T -Test /^Wilcoxon rank sum test is used to calculate the P-value.
^^Chi-square test is used to calculate the P-value.
$ Cox proportional hazards regression analysis used to calculate HR and p-value.
$* Generalized linear model is used to calculate estimates and p-value.

3.3. Oxygenation and hemodynamic (HD) Parameters

In the case of patients who were administered ketamine during their stay in the intensive care units (ICUs), there was a noteworthy enhancement in the PaO2/FiO2 ratio 24 hour after the initiation of ketamine compared to the reading taken 6 hours prior to its initiation (124.9 (92.1, 184.5) vs. 106 (73.1, 129.3); p-value = 0.002). However, there were no statistically significant variations in the vasoactive inotropic score (VIS) and the mean arterial pressure (MAP) between the two time points, i.e., Six hours before the utilization of ketamine and 24 hours after its administration (as indicated in Table 4). Conversely, the average time required for lactic acid levels to normalize was significantly shorter in patients who received ketamine when compared to the control group (beta coefficient (95 % CI): −1.55 (−2.42,−0.69), p-value = 0.0004) (as presented in Table 2)

3.4. 30-Day and hospital mortality

In the crude analysis, there was no substantial distinction in 30-day mortality rates (54.8 % vs. 50.9 %, p-value = 0.57) and in-hospital mortality rates (59.8 % vs. 59.3 %, p-value = 0.94) observed between patients who were administered ketamine and those in the control group. Furthermore, after conducting a Cox proportional hazard regression analysis, no statistically significant disparities were identified in 30-day mortality (HR 1.24; 95 % CI 0.86, 1.78, p-value = 0.25) and in-hospital mortality (HR 1.12; 95 % CI 0.87, 1.71, p-value = 0.25) between the two groups (as detailed in Table 2).

3.5. Complications during ICU stay

Patients who received ketamine displayed a reduced occurrence of hospital-acquired infections in comparison to those in the control group. Nevertheless, this difference did not reach statistical significance (OR 0.49; 95 % CI 0.22, 1.08, p-value = 0.07). Conversely, there were no statistically noteworthy distinctions between the two groups regarding other complications that occurred during their ICU stay. These included the emergence of new-onset atrial fibrillation, acute kidney injury (AKI), liver injury, and instances of thrombosis (Table 3).

4. Discussion

This multicenter cohort trial is one of the few studies conducted to assess the effectiveness and safety of ketamine use among mechanically ventilated critically ill patients with COVID-19 using propensity score matching. Balancing sedation is vital in ICU settings as excessive use of

Table 3
The ICU complications during stay.

Outcomes∆			P-value^^	Odds Ratio (OR) (95 %CI)	P-value $
	Control	Ketamine based			
New onset A fib., n (%)	23 (13.1)	6 (6.8)	0.13^^	0.49 (0.190,1.242)	0.13
Acute kidney injury, n(%)	84 (47.7)	44 (50.0)	0.73^^	1.11 (0.643,1.913)	0.71
Liver injury, n (%)	18 (10.2)	12 (13.6)	0.41^^	1.39 (0.635,3.050)	0.41
All thrombosis cases, n(%)	8 (4.5)	8 (9.1)	0.15^^	1.39 (0.668,2.891)	0.38
Hospital acquired Infection, n (%)	33 (18.8)	9 (10.2)	0.07^^	0.49 (0.224,1.083)	0.07

∆ Denominator of the percentage is the total number of patients.
^^ Chi-square test is used to calculate the P-value.
$ Logistic regression is used to calculate the OR and p-value.

Table 4
Oxygenation and HD parameters pre-and 24-hours post Ketamine administration.

Oxygenation/HD parameters ∆	Up to 6-hour pre-ketamine	24-hours post-ketamine	Delta	P-value^
PaO2/FiO2 ratio, Median (Q1, Q3)	106 (73.1, 129.3)	124.9 (92.1, 184.5)	22.5 (−10.0, 70.0)	0.002
Vasoactive Inotropic Score (VIS), Mean (SD)	14.1 (±58.6)	20.2 (±82.9)	4.94 (±66.8)	0.87
Mean arterial pressure (MAP), Median (Q1, Q3)	76.3 (68.0, 89.0)	79.5 (70, 88.5)	−1.50 (−13.0, 9.6)	0.26

∆ represents patients who received inhaled Ketamine.
^ Wilcoxon rank sum test is used to calculate the P-value.

sedatives may compromise the PaO2/FiO2 ratio, impacting respiratory function which could be translated to worse ICU related outcomes. Furthermore, in this study we investigated the impact of ketamine use among these patients and its effect on their ICU length of stay, improvement in oxygenation and hemodynamic parameters 24 hours after Ketamine use, time for lactic acid normalization, MV duration, mortality, hospital length of stay and ICU- complications such as (new-onset atrial fibrillation, thrombosis, acute kidney injury (AKI), liver injury, hospital-acquired infection, and secondary fungal infection.

This study illustrated that patients in the ketamine group had shorter ICU length of stay, numerically. Moreover, the patients in the ketamine group had shorter overall hospital LOS. This might be explained by the interesting properties of ketamine as an immunomodulator and its ability to reduce inflammatory cytokines such as IL-6 (De Kock et al., 2013), which is known to be elevated during COVID-19 illness (cytokine storming) and was found to be associated with an increased risk of mortality (Shekhawat et al., 2021). Another factor that might have contributed to our findings of shorter length of hospital stay could be related to reduced incidence of delirium with low doses of ketamine (Perbet et al., 2018). These results were inconsistent with the results of the Pata et al. (Pata et al., 2021) study, which reported that patients in the ketamine group had longer hospital stays due to neurocognitive perturbation.

In critically ill patients with COVID-19, maintaining ventilation and oxygenation remains a major challenge. In our study, we observed that patients in the ketamine group had a higher rate of PaO2/FiO2 24 hours post-ketamine initiation. It is plausible to believe that the high P/F ratio observed in patients who received ketamine could have led to improvement in intrapulmonary gaseous exchange, overall improvement in ARDS, and shortened length of hospital stay (Park et al., 2016). The P/F ratio is an objective measure of lung function and is a prognostic marker of ICU outcomes and length of hospital stay (Cooke et al., 2008; de Jonge et al., 2008).

Furthermore, we witnessed that the median time that patients in the ketamine group spent using a mechanical ventilator was 11 days. The duration of mechanical ventilation was comparable to the median time of 7 days in the ketamine group studied by Amer et al. (Amer et al., 2021). However, it needs to be highlighted that the higher median duration of mechanical ventilation in our cohort could be due to the severe nature of the disease and its negative impact on the lung tissues. It is important to note that the majority of the study participants by Amer et al. were from the medical ICU and had lower disease burdens than the general population. (Amer et al., 2021). Moreover, upon comparing the severity of illness within our study population, we noted a higher median APACHE II score of 19.5 (with a range of 12–27), contrasted with the findings of Garner et al., where the median was 14 (with a range of 3–28). (Garner et al., 2021).

In this cohort, we found that ketamine did not inversely affect the hemodynamic parameters of patients with severe ARDS. Additionally, patients in the ketamine group had a shorter time to normalize lactic acid. This could be contributed to multiple factors such as the improvement of perfusion, increasing oxygenation through MV and the aid of ketamine in increasing blood pressure, heart rate and in turn cardiac output through its central sympathetic stimulation which might help in clearing lactate through liver and kidney by improving the blood perfusion to these organs. (Craven, 2007; Lexicomp, n.d.).The vasopressor requirements in our study were evaluated and calculated using vasoactive inotropic score (VIS) 6 hours before ketamine administration and 24 hours after that and we notice that there was no difference on the vasoactive inotropic score (VIS) or the mean arterial pressure (MAP) between the two time points, this is could be influenced by the other sedative used along with ketamine such as propofol which is known to adversely affect the blood pressure and heart rate (Lexicomp, n.d.), but we didn't compare it to the control group. These findings are consistent with Amer et al. (Amer et al., 2021) study that reported no increase in vasopressor requirements among patients who were sedated using ketamine. Given its attractive properties, ketamine can be contemplated to be used for COVID-19 and other hyperinflammatory disease states such as septic shock due to their pathophysiological similarities. (Weinbroum, 2021).

Notably, ketamine use had no effect on 30 days mortality or hospital mortality, which was comparable to previous findings reported by Chan (Chan et al., 2022) et al. However, these results conflict with Pata et al (Pata et al., 2021) previous findings as patients in the ketamine group had lower mortality with unexplained mechanisms. Our study was likely underpowered to detect a statistically significant mortality difference between patients receiving ketamine and controls. However, there was a trend toward a slightly higher percentage of mortality in cohorts that received ketamine. We believe that this slighter greater mortality can be explained by the clinical progression of the disease itself after ICU admission and/or inadequate treatment response.

Similar to our finding, Pata (Pata et al., 2021) and his colleagues found that patients who were sedated with ketamine had a lower incidence of hospital-acquired infection. This can be explained by the immunomodulatory activity of ketamine; it has been shown to antagonize inflammatory responses and reduce proinflammatory cytokine production, such as reduced IL-6 and TNFα production (Yuhas et al., 2015). ketamine has also been demonstrated to be involved in the growth-inhibiting activity of serious infections acquired in hospitals, such as methicillin-resistant *Staphylococcus aureus* (MRSA). (Coutinho et al., 2021). Also, our cohort's reduced length of hospital stay might have contributed to the overall risk of acquiring hospital infection owing to less exposure.

Our study's notable strengths lie in its multicenter design, combining

both retrospective and prospective approaches. It stands out as one of the limited studies investigating the effects of ketamine on COVID-19. Moreover, we employed rigorous analytical methods such as propensity score matching and multiple regression to mitigate potential biases.. Nevertheless, our study has some limitations that need to be addressed. It was retrospective-prospective in nature, and the risk for residual confounders cannot be ruled out due to the missing documentation and due to limited follow-up time long-term complications such as neurocognitive dysfunction could not be assessed. Due to the nature of our study, we can assume association and not causality for the use of ketamine as an adjunct sedative compared to the control group. Despite some imporovement in the clinical outcomes, ketamine use is still controversial as larger prospective studies are recommended to be conducted to assess the safety and effectiveness of ketamine as a sedative in critically ill adult patients.

5. Conclusion

Ketamine-based sedation is associated with shorter hospital LOS, improved PaO2/FiO2 ratio 24-hours post ketamine, and faster lactic acid normalization but no mortality benefits in critically ill patients with COVID-19 patients. Thus, larger prospective studies are recommended to assess the safety and effectiveness of ketamine as a sedative in critically ill adult patients.

Author Contributions

Ohoud Aljuhani and Khalid Al Sulaiman equally contributed to the conception and design of the research and project administration. Ghazwa B. Korayem and Ali F. Altebainawi contributed to the acquisition and analysis of the data. Abdulrahman Alshaya, Majed Nahari, Bodoor S. Al-Dosari, Lina I. Alnajjar contributed to Writing – original draft, Writing – review & editing. Abeer A.Alenazi, Samiah Alsohimi, Mashael Alfaifi contributed to Supervision, Resources, Project administration and Software. Khuzama Alsamnan, Munirah A. Alkathiri, Nora AlQussair, Reem M. Alanazi, Munirah F. Alhmoud, Nadin L. Alanazi, Aljawharah M. Alenez contributed to Data curation, Writing – original draft, Writing – review & editing, Validation. Hadeel Alkofide, Ramesh Vishwakarma have contributed equally to Methodology, Investigation, Validation, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We extend our gratitude to the entire support team from the Saudi critical care pharmacy research (SCAPE) platform and the Saudi Society for Multidisciplinary Research Development and Education Society for their invaluable assistance with this project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2024.102061.

References

Al Harbi, S., Kensara, R., Aljuhani, O., Korayem, G.B., Altebainawi, A.F., Al Harthi, A., Vishwakarma, R., Alenazi, A.M., Almutairi, A., Alshaya, O., Alraddadi, S., Al Sulaiman, T., Aldakkan, L., Mahboob, R., Alaamer, K., Alissa, A., Hafiz, A., Aldhayyan, N., Althewaibi, S., Alenezi, F., Alkhotani, N.Y., Alghamdi, S.A., Alenazi, A.A., Al Sulaiman, K., 2022. Statins and risk of thrombosis in critically ill patients with COVID-19: A multicenter cohort study. Clin. Appl. Thromb. 28 https://doi.org/10.1177/10760296221103864.

Al Sulaiman, K., Aljuhani, O., Al Shaya, A.I., Kharbosh, A., Kensara, R., Al Guwairy, A., Alharbi, A., Algarni, R., Al Harbi, S., Vishwakarma, R., Korayem, G.B., 2021a. Evaluation of zinc sulfate as an adjunctive therapy in COVID-19 critically ill patients: A two center propensity-score matched study. Crit. Care 25. https://doi.org/10.1186/s13054-021-03785-1.

Al Sulaiman, K.A., Aljuhani, O., Eljaaly, K., Alharbi, A.A., Al Shabasy, A.M., Alsaeedi, A. S., Al Mutairi, M., Badreldin, H.A., Al Harbi, S.A., Al Haji, H.A., Al Zumai, O.I., Vishwakarma, R.K., Alkatheri, A., 2021b. Clinical features and outcomes of critically ill patients with coronavirus disease 2019 (COVID-19): A multicenter cohort study. Int. J. Infect. Dis. 105, 180–187. https://doi.org/10.1016/j.ijid.2021.02.037.

Al Sulaiman, K., Aljuhani, O., Korayem, G.B., Hafiz, A., Alalawi, M., Badreldin, H.A., Altebainawi, A.F., Vishwakarma, R., Alissa, A., Alghamdi, A., Alenazi, A.A., Al Enazi, H., Alanazi, S., Alhammad, A., Alghamdi, J., AlFaifi, M., Al Sehli, F.A., Aldossari, M.A., Alhubaishi, A.A., Al-Ali, A.Y., Al-Dorzi, H.M., 2022a. Standard dosing of enoxaparin versus unfractionated heparin in critically ill patient with COVID-19: A multicenter propensity-score matched study. Thromb. J. 20 https://doi.org/10.1186/s12959-022-00432-9.

Al Sulaiman, K., Korayem, G.B., Altebainawi, A.F., Al Harbi, S., Alissa, A., Alharthi, A., Kensara, R., Alfahed, A., Vishwakarma, R., Al Haji, H., Almohaimid, N., Al Zumai, O., Alrubayan, F., Asiri, A., Alkahtani, N., Alolayan, A., Alsohimi, S., Melibari, N., Almagthali, A., Aljahdali, S., Alenazi, A.A., Alsaeedi, A.S., Al Ghamdi, G., Al Faris, O., Alqahtani, J., Al Qahtani, J., Alshammari, K.A., Alshammari, K.I., Aljuhani, O., 2022b. Evaluation of inhaled nitric oxide (iNO) treatment for moderate-to-severe ARDS in critically ill patients with COVID-19: A multicenter cohort study. Crit. Care 26. https://doi.org/10.1186/s13054-022-04158-y.

Aljuhani, O., Al Sulaiman, K., Alshabasy, A., Eljaaly, K., Al Shaya, A.I., Noureldeen, H., Aboudeif, M., Al Dosari, B., Alkhalaf, A., Korayem, G.B., Aleissa, M.M., Badreldin, H. A., Al Harbi, S., Alhammad, A., Vishwakarma, R., 2021. Association between tocilizumab and emerging multidrug-resistant organisms in critically ill patients with COVID-19: A multicenter, retrospective cohort study. BMC Infect. Dis. 21, 1127. https://doi.org/10.1186/s12879-021-06813-1.

Amer, M., Maghrabi, K., Bawazeer, M., Alshaikh, K., Shaban, M., Rizwan, M., Amin, R., De Vol, E., Baali, M., Altewerki, M., Bano, M., Alkhaldi, F., Alenazi, S., Hijazi, M., 2021. Adjunctive ketamine for sedation in critically ill mechanically ventilated patients: an active-controlled, pilot, feasibility clinical trial. J. Intensive Care 9, 1–12. https://doi.org/10.1186/s40560-021-00569-1.

Arentz, M., Yim, E., Klaff, L., Lokhandwala, S., Riedo, F.X., Chong, M., Lee, M., 2020. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. JAMA - J. Am. Med. Assoc. 323, 1612–1614. https://doi.org/10.1001/jama.2020.4326.

Bawazeer, M., Amer, M., Maghrabi, K., Alshaikh, K., Amin, R., Rizwan, M., Shaban, M., De Vol, E., Hijazi, M., 2020. Adjunct low-dose ketamine infusion vs standard of care in mechanically ventilated critically ill patients at a Tertiary Saudi Hospital (ATTAINMENT trial): Study protocol for a randomized, prospective, pilot, feasibility trial. Trials 21. https://doi.org/10.1186/s13063-020-4216-4.

Breen, D., Karabinis, A., Malbrain, M., Morais, R., Albrecht, S., Jarnvig, I.L., Parkinson, P., Kirkham, A.J.T., 2005. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomised trial [ISRCTN47583497]. Crit. Care 9, R200. https://doi.org/10.1186/CC3495.

Chan, K., Burry, L.D., Tse, C., Wunsch, H., De Castro, C., Williamson, D.R., 2022. Impact of ketamine on analgosedative consumption in critically ill patients: A systematic review and meta-analysis. Ann. Pharmacother. 56, 1139–1158. https://doi.org/10.1177/10600280211069617.

Chang, Y., Chen, T.L., Sheu, J.R., Chen, R.M., 2005. Suppressive effects of ketamine on macrophage functions. Toxicol. Appl. Pharmacol. 204, 27–35. https://doi.org/10.1016/j.taap.2004.08.011.

Cooke, C.R., Kahn, J.M., Caldwell, E., Okamoto, V.N., Heckbert, S.R., Hudson, L.D., Rubenfeld, G.D., 2008. Predictors of hospital mortality in a population-based cohort of patients with acute lung injury. Crit. Care Med. 36, 1412–1420. https://doi.org/10.1097/CCM.0b013e318170a375.

Coutinho, T.D.N.P., Barroso, F.D.D., da Silva, C.R., da Silva, A.R., Cabral, V.P.de.F., Valente Sá, L.G.D.A., Cândido, T.M., da Silva, L.J., Ferreira, T.L., da Silva, W.M.B., Silva, J., Marinho, E.S., Cavalcanti, B.C., de Moraes, M.O., Nobre Júnior, H.V., Neto, J.B.A., 2021. Effects of ketamine in methicillin-resistant staphylococcus aureus and in silico interaction with sortase a. Can. J. Microbiol. 67, 885–893. https://doi.org/10.1139/cjm-2021-0093.

Craven, R., 2007. Ketamine. Anaesthesia 62, 48–53. https://doi.org/10.1111/j.1365-2044.2007.05298.x.

de Jonge, E., Peelen, L., Keijzers, P.J., Joore, H., de Lange, D., van der Voort, P.H.J., Bosman, R.J., de Waal, R.A.L., Wesselink, R., de Keizer, N.F., 2008. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit. Care 12. https://doi.org/10.1186/cc7150.

De Kock, M., Loix, S., Lavand'homme, P., 2013. Ketamine and peripheral inflammation. CNS Neurosci. Ther. 19, 403–410. https://doi.org/10.1111/cns.12104.

Faust, A.C., Rajan, P., Sheperd, L.A., Alvarez, C.A., McCorstin, P., Doebele, R.L., 2016. Impact of an analgesia-based sedation protocol on mechanically ventilated patients in a medical intensive care unit. Anesth. Analg. 123, 903–909. https://doi.org/10.1213/ANE.0000000000001393.

Fernando, S.M., Ferreyro, B.L., Urner, M., Munshi, L., Fan, E., 2021. Diagnosis and management of acute respiratory distress syndrome. CMAJ 193, E761–E768. https://doi.org/10.1503/cmaj.202661.

Garg, K., Grewal, G., Grewal, A., Singh, A., Mishra, A., Singh Nar, A., Bawa, A., 2013. Hemodynamic responses with different dose of ketamine and propofol in day care gynecological surgeries. J. Clin. Diagnostic Res. 7, 2548–2550. https://doi.org/10.7860/JCDR/2013/6860.3607.

Garner, O., Patterson, J., Mejia, J.M., Anand, V., Deleija, J., Nemeh, C., Vallabh, M., Staggers, K.A., Howard, C.M., Treviño, S.E., Siddique, M.A., Morgan, C.K., 2021. Impact of ketamine as an adjunct sedative in acute respiratory distress syndrome due to COVID-19 Pneumonia. Respir. Med. 189 https://doi.org/10.1016/j.rmed.2021.106667.

Grasselli, G., Zangrillo, A., Zanella, A., Antonelli, M., Cabrini, L., Castelli, A., Cereda, D., Coluccello, A., Foti, G., Fumagalli, R., Iotti, G., Latronico, N., Lorini, L., Merler, S., Natalini, G., Piatti, A., Ranieri, M.V., Scandroglio, A.M., Storti, E., Cecconi, M., Pesenti, A., 2020. Baseline Characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA - J. Am. Med. Assoc. 323, 1574–1581. https://doi.org/10.1001/jama.2020.5394.

Groth, C.M., Droege, C.A., Connor, K.A., Kaukeinen, K., Acquisto, N.M., Chui, S.H.J., Cucci, M.D., Dixit, D., Flannery, A.H., Gustafson, K.A., Glass, N.E., Horng, H., Heavner, M.S., Kinney, J., Kruer, R.M., Peppard, W.J., Sarangarm, P., Sikora, A., Viswesh, V., Erstad, B.L., 2022. Multicenter retrospective review of ketamine use in the ICU. Crit. Care Explor. 4, e0633.

Guan, W., Ni, Z., Hu, Yu., Liang, W., Ou, C., He, J., Liu, L., Shan, H., Lei, C., Hui, D.S.C., Du, B., Li, L., Zeng, G., Yuen, K.-Y., Chen, R., Tang, C., Wang, T., Chen, P., Xiang, J., Li, S., Wang, J.-L., Liang, Z., Peng, Y., Wei, L., Liu, Y., Hu, Y.-H., Peng, P., Wang, J.-M., Liu, J., Chen, Z., Li, G., Zheng, Z., Qiu, S., Luo, J., Ye, C., Zhu, S., Zhong, N., 2020. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 382, 1708–1720. https://doi.org/10.1056/nejmoa2002032.

Hasan, S.S., Capstick, T., Ahmed, R., Kow, C.S., Mazhar, F., Merchant, H.A., Zaidi, S.T.R., 2020. Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroids use: A systematic review and meta-analysis. Expert Rev. Respir. Med. 14, 1149–1163. https://doi.org/10.1080/17476348.2020.1804365.

Hirota, K., Sato, T., Rabito, S.F., Zsigmond, E.K., Matsuki, A., 1996. Relaxant effect of ketamine and its isomers on histamine-induced contraction of tracheal smooth muscle. Br. J. Anaesth. 76, 266–270. https://doi.org/10.1093/bja/76.2.266.

Kam, P.C.A., Cardone, D., 2007. Propofol infusion syndrome. Anaesthesia 62, 690–701. https://doi.org/10.1111/j.1365-2044.2007.05055.x.

Kolawole, I.K., 2001. Ketamine hydrochloride: A useful but frequently misused drug. Niger. J. Surg. Res. 3, 118–125. https://doi.org/10.4314/njsr.v3i3.12232.

Kress, J.P., Hall, J.B., 2006. Sedation in the mechanically ventilated patient. Crit. Care Med. 34 https://doi.org/10.1097/01.CCM.0000239117.39890.E3.

Kurdi, M., Theerth, K., Deva, R., 2014. Ketamine: Current applications in anesthesia, pain, and critical care. Anesth. Essays Res. 8, 283. https://doi.org/10.4103/0259-1162.143110.

Lexicomp [WWW Document], n.d. URL https://online.lexi.com (accessed 10.17.22).

Marra, A., Ely, E.W., Pandharipande, P.P., Patel, M.B., 2017. The ABCDEF bundle in critical care. Crit. Care Clin. 33, 225–243. https://doi.org/10.1016/j.ccc.2016.12.005.

Miller, A.C., Jamin, C.T., Elamin, E.M., 2011. Continuous intravenous infusion of ketamine for maintenance sedation [WWW document]. Minerva Anestesiol.

Nehama, J., Pass, R., Bechtler-Karsch, A., Steinberg, C., Notterman, D.A., 1996. Continuous ketamine infusion for the treatment of refractory asthma in a mechanically ventilated infant: Case report and review of the pediatric literature. Pediatr. Emerg. Care 12, 294–297. https://doi.org/10.1097/00006565-199608000-00015.

Pabelick, C.M., Jones, K.A., Street, K., Lorenz, R.R., Warner, D.O., 1997. Calcium concentration-dependent mechanisms through which ketamine relaxes canine airway smooth muscle. Anesthesiology 86, 1104–1111. https://doi.org/10.1097/00000542-199705000-00014.

Park, J.H., Lee, J.S., Lee, J.H., Shin, S., Min, N.H., Kim, M.S., 2016. Effect of the prolonged inspiratory to expiratory ratio on oxygenation and respiratory mechanics during surgical procedures. Med. (United STATES) 95, e3269.

Pata, R., Sandeep, P., Aung, H.M., Patel, M.J., Dolkar, T., Nway, N., Bhanu, K., Ahmady, A., Kiani, R., Swaroop, R., Schmidt, F., Enriquez, D., 2021. Ketamine infusion as a sedative-analgesic in severe ARDS (KISS). J. Community Hosp. Intern. Med. Perspect. 11, 619–623. https://doi.org/10.1080/20009666.2021.1948669. PMID: 19874582.

Perbet, S., Verdonk, F., Godet, T., Jabaudon, M., Chartier, C., Cayot, S., Guerin, R., Morand, D., Bazin, J.E., Futier, E., Pereira, B., Constantin, J.M., 2018. Low doses of ketamine reduce delirium but not opiate consumption in mechanically ventilated and sedated ICU patients: A randomised double-blind control trial. Anaesth. Crit. Care Pain Med. 37, 589–595. https://doi.org/10.1016/j.accpm.2018.09.006.

Sato, T., Hirota, K., Matsuki, A., Zsigmond, E.K., Rabito, S.F., 1998. The role of the N-methyl-D-Aspartic acid receptor in the relaxant effect of ketamine on Tracheal smooth muscle. Anesth. Analg. 87, 1383–1388. https://doi.org/10.1097/00000539-199812000-00033.

SCAPE, n.d. Saudi Critical Care Pharmacy Research [WWW Document]. URL https://www.scape-platform.com/.

Shekhawat, J., Gauba, K., Gupta, S., Purohit, P., Mitra, P., Garg, M., Misra, S., Sharma, P., Banerjee, M., 2021. Interleukin-6 perpetrator of the COVID-19 cytokine storm. Indian J. Clin. Biochem. 36, 440–450. https://doi.org/10.1007/s12291-021-00989-8.

Uludağ, Ö., Doğukan, M., Kaya, R., Tutak, A., Dumlupınar, E., 2020. Comparison of the effects of midazolam-ketamine or midazolam-propofol combinations on hemodynamic stability, patient comfort, and post-anesthesia recovery in children undergoing sedation for magnetic resonance imaging procedures. Ain-Shams J. Anesthesiol. 12, 1–7. https://doi.org/10.1186/s42077-019-0037-7.

Umunna, B.P., Tekwani, K., Barounis, D., Kettaneh, N., Kulstad, E., 2015. Ketamine for continuous sedation of mechanically ventilated patients. J. Emergencies, Trauma Shock 8, 11–15. https://doi.org/10.4103/0974-2700.145414.

Weinbroum, A.A., 2021. Perspectives of ketamine use in COVID-19 patients. J. Korean Med. Sci. 36 https://doi.org/10.3346/jkms.2021.36.e28.

Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., Xu, L., Zhou, F., Jiang, J., Bai, C., Zheng, J., Song, Y., 2020. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern. Med. 180, 934–943. https://doi.org/10.1001/jamainternmed.2020.0994.

Yuhas, Y., Ashkenazi, S., Berent, E., Weizman, A., 2015. Immunomodulatory activity of ketamine in human astroglial A172 cells: Possible relevance to its rapid antidepressant activity. J. Neuroimmunol. 282, 33–38. https://doi.org/10.1016/j.jneuroim.2015.03.012.

Zhu, M.M., Qian, Y.N., Zhu, W., Xu, Y.M., Rong, H.B., Ding, Z.N., Fu, C.Z., 2007a. Protective effects of ketamine on allergen-induced airway inflammatory injure and high airway reactivity in asthma: Experiment with rats [WWW document]. Natl. Med. J. China.

Zhu, M.M., Zhou, Q.H., Zhu, M.H., Bo Rong, H., Xu, Y.M., Qian, Y.N., Fu, C.Z., 2007b. Effects of nebulized ketamine on allergen-induced airway hyperresponsiveness and inflammation in actively sensitized Brown-Norway rats. J. Inflamm. 4 https://doi.org/10.1186/1476-9255-4-10.