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REVIEW ARTICLE

Ketamine Infusion as a Single Sedative Agent for Post-Intubation Management of Critically Ill Patients: A Systematic Review and Meta-Analysis

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Abstract: **Introduction:** Combining multiple drugs for intubation raises concerns such as increased side effects, medication errors, nursing workload, and costs. Ketamine, with its anesthetic and analgesic properties, shows promise as a sedative agent for post-intubation care. This study aimed to evaluate the efficacy and safety of ketamine infusion as the sole sedative for critically ill intubated patients. **Methods:** Following PRISMA 2020 guidelines, we conducted a systematic review by searching Ovid MEDLINE, Cochrane Central Register of Controlled Trials, and Google Scholar up to May 10, 2024. We included studies assessing ketamine use for post-intubation sedation in critically ill adults or children. Study quality was assessed using the Newcastle–Ottawa scale, and meta-analysis was performed using a random-effects model. **Results:** The systematic review included 7 studies, with 4 studies included in the meta-analysis. There was no significant difference in mortality (OR = 1.52; 95% CI: 0.49–4.70, p = 0.46; I2 = 83%) or length of hospital stay (MD = 6.42; 95% CI: -1.42-14.26, p = 0.11; I2 = 84%) between the ketamine only and other groups. The most common adverse events in the ketamine infusion group were atrial fibrillation and agitation. **Conclusion:** Single-agent ketamine infusion is effective and safe for critically ill intubated patients. No significant differences were found in mortality or hospital stay between ketamine only and other groups. Atrial fibrillation and agitation were the most common adverse effects.

Keywords: Ketamine; mechanical ventilation; sedation; critical illness; medication

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1. Introduction

Critically ill patients with respiratory failure, hemodynamic instability due to medical or traumatic causes or severe neurologic impairment frequently require endotracheal intubation and placement on mechanical ventilation (MV) in the emergency department (ED)(1–3). A recent study showed that out of nearly 6.5 million patients in the United States, 2.8% received mechanical ventilation after being hospitalized, and the overall mortality rate was 34.5% (1). Patients placed on MV often experience discomfort and psychological distress, requiring the use of sedatives and analgesic agents for patient comfort (2,4,5). Commonly used sedation medications such as etomidate, propofol, and midazolam have a short onset of action and work on gamma-aminobutyric acid (GABA) receptors (2,4,5). All of these agents have potential limitations, including adrenal suppression (etomidate)(4), propofol infusion syndrome (5), and withdrawal symptoms (midazolam)(2). None of these medications has analgesic properties requiring the addition of agents such as opioids. In critical illness, opioids are associated with an increased risk of delirium (6,7), an increased risk of ventilator-acquired pneumonia(8), and acute opioid withdrawal syndrome (9).

Ketamine is a dissociative anesthetic that antagonizes the glutamate NMDA receptors, producing dissociative anesthesia and interrupting the thalamocortical system, which is characterized by analgesia and dissociation. It was synthesized in 1962 from phencyclidine and developed as a safer anesthetic with fewer hallucinogenic effects. Approved for medical use in 1970, it became widely used in both veterinary and human medicine, including surgical anesthesia during the Vietnam War. Its dissociative properties and hemodynamic stability have led to its integration into critical care,

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and it is now recognized as an essential medicine by the WHO (10,11). Complications associated with ketamine include hypersalivation, hyperreflexia, hypertonicity, increased intraocular pressure, vomiting, delirium, and agitation (10).
A recent review and meta-analysis on the usage of ketamine in mechanically ventilated patients was recently published (12). This review encompasses a comprehensive analysis of multiple studies that investigated the use of ketamine as a continuous infusion for adjunctive analgosedation in mechanically ventilated critically ill patients rather than as a standalone agent. Based on a scoping review, we formulated the hypothesis that the efficacy and safety of ketamine could be indirectly influenced when used as an adjunctive agent in combination with other substances. Consequently, the assessment of ketamine efficacy may be impeded when administered concurrently with other agents, highlighting the necessity of evaluating its efficacy as a singular agent. Hence, the objective of this study was to systematically assess the efficacy and safety of ketamine infusion as a standalone sedative agent for post intubation care of critically ill patients, both with and without comparisons to other sedative agents such as etomidate, propofol, thiopental, or midazolam.

2. Methods

2.1. Protocol and rregistration

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (13,14). The study protocol was registered in the PROSPERO international prospective registry (CRD42022313091) but was not subjected to independent peer review prior to registration. Ethical approval was not required.

2.2. Data sources and search strategy

With the assistance of an experienced health sciences librarian, we developed a comprehensive search strategy across multiple databases. The primary search was conducted in Ovid MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science (ISI) to ensure a broad and inclusive literature search. We also searched Google Scholar for additional grey literature and relevant studies. The search was conducted up to Feb 10, 2025. Additionally, we manually screened reference lists of relevant meta-analyses, systematic reviews, and cohort studies to identify further eligible articles.
No restrictions were applied regarding language or country of publication. The detailed search strategy used for each database is provided in Appendix 1.

2.3. Study selection

Two independent reviewers screened all titles, abstracts, and full-text articles using predefined inclusion and exclusion criteria to minimize selection bias. Disagreements were resolved through discussion or consultation with a third reviewer to ensure objective selection. The inclusion criteria can be described as PICO: 1) P (Population): Adult or pediatric critically ill patient intubated in the prehospital setting, the ED or ICU and connected to mechanical ventilator 2) I (Intervention): ketamine infusion as a single agent; 3) C (Comparison): either alone or in combination with propofol, etomidate, thiopental, midazolam, Methohexital, Dexmedetomidine, Fentanyl; 4) O (Outcome): efficacy and safety. We omitted abstracts, letters, conference papers, case reports, reviews, and research that were unavailable as full text. We excluded studies if ketamine was used for a different indication, such as resistant depression and studies in which ketamine was used in conjunction with other drugs or as an adjunctive agent.

2.4. Data extraction and quality assessment of studies

The studies were exported to the EndNote Reference Library version 20.0.1 (Clarivate Analytics) software; it was used for data management due to its robust capabilities in identifying and removing duplicate records, organizing citations, and streamlining the screening process, enhancing accuracy and efficiency. Two reviewers extracted data and assessed the quality of included studies concurrently and independently. Disagreements between reviewers regarding study quality assessment were resolved through discussion. If consensus was not reached, a third investigator or a senior author provided adjudication. The Newcastle-Ottawa Scale (NOS) was used to grade the cohort studies' quality (15). NOS score 1-5 was considered as high risk for bias, 6-7 was moderate, and score >7 was considered low risk of bias.

2.5. Data Synthesis and Statistical Analysis

Data were extracted using the MS Excel sheet (mean, standard deviations, and endpoint events). Missing data were managed according to protocols and any other methods deemed suitable by the authors. RevMan 5.4 (Cochrane Collaboration, 2020) was used to conduct quantitative analysis with a random-effects model to measure the mortality outcomes and length of hospital stay for patients in the ketamine and no-ketamine groups. A random-effects model was selected for meta-analysis due to the anticipated clinical and methodological heterogeneity among the included studies. Given variations in patient populations (adult vs. pediatric), study settings (ICU vs. ED), and ketamine dosing protocols, a random-effects model was preferred as it accounts for both within-study and between-study variability, providing a more conservative and generalizable estimate of effect size.
Forest plots were created to illustrate pooled estimates. Given the marked heterogeneity between the evaluation criteria and results between the included studies for adverse events and efficacy, performing a meta-analysis would be inappropriate. We have elected to present the unpoled data for

information.

Continuous data was pooled as mean difference (MD), and its 95% confidence interval (CI), and dichotomous data was used as odds ratio (OR) and its 95% CI. Heterogeneity was evaluated using I2 (I2 50% or p < 0.1 indicative of high heterogeneity). Moreover, P< 0.05 is considered statistically significant.

In this study, efficacy was operationally defined as the ability of ketamine administration to produce sedative effects. A Richmond agitation sedation scale of -2 to 0 has been advocated in this patient population to minimize sedation. This strategy reduces mortality and decreases the duration of mechanical ventilation and the length of stay in the ICU.

3. Results

3.1. Literature search results

The preliminary search identified 1322 relevant studies and trial registries. Following exclusions based on titles and abstracts, 60 full-text articles were evaluated to determine their suitability for inclusion. Seven papers were retained for qualitative analysis. The findings of our literature search are summarized in Figure 1.

3.2. Study characteristics

Table 1 in the supplements summarizes the seven included studies (4 studies with adult patients; 2 with pediatric patients; 1 mixed population). All seven cohort studies reported data on the use of ketamine for mechanically ventilated patients (16–22). One study included adult patients in the ICU requiring a norepinephrine infusion and sedation (17). Two studies had enrolled patients who required ketamine, regardless of admitting diagnosis (21,22). In another study, participants with moderate to severe acute respiratory distress syndrome (ARDS) caused by COVID-19 were enrolled (21). One study involved only adult patients who had been diagnosed with septic shock (20). Another study selected patients diagnosed with refractory bronchospasm from the pediatric intensive care unit (PICU) (16), and another selected critically ill patients from the PICU with a variety of different diagnoses (18).

3.3. Quality assessment and publication bias

Table 2 shows the assessment of quality and risk of bias. Because we identified less than 10 studies for inclusion in this systematic review and meta-analysis, we could not assess publication bias. None of the studies were identified as low quality or high risk of bias.

3.4. Outcomes

Efficacy

In all articles, the nurses mainly evaluated the effectiveness of ketamine as a standalone treatment using the RAAS If the desired RAAS target was not achieved using ketamine alone, an additional agent would be introduced.

The efficacy was reported in four studies; Shurtleff et al. reported that patients in the ketamine group had a lower median percentage of RASS scores at goal (70% [IQR: 47%-87%] vs. 84% [IQR: 68%-93%]; P= 0.019). However, in patients with available pain scores (n = 32), the ketamine group appeared to have a higher percentage scores at goal (99% [IQR: 93%-100%] vs. 91% [IQR: 77%-96%]; P = 0.044) (21). Pata et al. reported that Ketamine was started with a loading dose of 0.5 mg/ kg intravenous bolus followed by 0.5 mg/kg/hr via continuous infusion, and target RAAS was achieved by titrated within the range of 0.2 to 1 mg/kg/hr (19). Reese et al. reported efficacy by achieving RASS goal range of 1 to -2, if continuous sedation was still necessary beyond 48 hours, patients were transitioned from ketamine to the standard ICU sedation protocol and attending physicians had the discretion to discontinue ketamine or introduce additional sedative and analgesic agents as deemed clinically necessary. They found that the ketamine group received less continuous analgesia and less benzodiazepine to achieve target RASS (20).

Park et al. reported that RASS sedation score decreased (0 vs. -1, P = 0.06) after continuous ketamine infusion, which might have been caused by an additional sedative effect of ketamine (18). We conclude that the continuous ketamine infusion is an effective single sedative agent in mechanically ventilated critically ill patients.

Mortality

In the four studies reporting data for mortality between ketamine and no-ketamine groups, one study demonstrated a decreased risk of mortality associated with ketamine (19), and one study showed an increased risk of mortality in the ketamine group (18). Two of the included studies demonstrated no significant difference between the ketamine and no-ketamine groups. Using a random effects model, the pooled risk of mortality in patients receiving ketamine was OR 1.52 (95% CI 0.49-4.7, p=0.46: I2=83%; Figure 2].

Hospital Length of Stay

In the four studies included in the meta-analysis, two studies demonstrated increased hospital length of stay associated with ketamine use (18,19). Two studies showed no difference in hospital length of stay between the ketamine and no-ketamine groups (20,21). Using a random effects model, no significant difference between the ketamine and no-ketamine groups was detected in the length of hospital stay [MD = 6.42; 95% CI: -1.42-14.26, p=0.11; I2=84%; Figure 2].

Adverse Events

In our systematic review, adverse events associated with ketamine infusion varied across studies. Umunna et al. reported new-onset atrial fibrillation in 2 out of 30 patients (6.7%) and agitation in 2 out of 30 patients (6.7%) (22). Reese et al. documented severe agitation in 1 out of 10 patients (10%) at 36 hours (20). Pata et al. did not report adverse events specifically linked to ketamine but found no significant differences between the ketamine and other groups

in vasopressor use, delirium, urinary tract infections (UTI), line-associated bloodstream infections (CLABSI), pneumonia, or acute kidney injury (19). Shurtleff et al. reported a high incidence of delirium, occurring in 37 out of 50 ketamine patients (74%) compared to 43 out of 50 other patients (85%), suggesting a lower but not statistically significant reduction in delirium with ketamine (21). Youssef-Ahmed et al. noted 2 adverse events in 5 pediatric patients (40%), including extensive tracheobronchial secretions and hallucinations (16). Sohaib Khatib et al. assessed hypotension using vasopressor requirements and found lower median norepinephrine needs in the ketamine group compared to propofol and midazolam, with this difference persisting at 1-, 3-, and 30-hours post-infusion (17). Park et al. were unable to assess adverse effects due to unsatisfactory records (18).

In summary, among ketamine-treated patients, atrial fibrillation and agitation each occurred in 6.7% (2/30), severe agitation was reported in 10% (1/10), and delirium was observed in 74% (37/50) of ketamine patients compared to 85% (43/50) in the other group. In pediatric patients, 40% (2/5) experienced adverse effects, including tracheobronchial secretions and hallucinations. Hemodynamic stability was generally preserved, with lower vasopressor requirements in the ketamine group. No significant differences were found in infection rates or kidney injury, though adverse event reporting varied across studies.

4. Discussion

In this systematic review and meta-analysis, we sought to measure the efficacy and safety of ketamine infusion as a single agent for post intubation management and analgesia requiring mechanical ventilation. Strictly adhering to the PRISMA guidelines for systematic reviews and employing a comprehensive search strategy, we identified seven relevant studies for inclusion and four that were appropriate for meta-analysis for the secondary outcome of mortality and length of hospital stay.

Based on our findings, ketamine was an effective single-agent sedative for post intubation management of mechanically ventilated critically ill patients. However, no significant differences were observed in mortality (OR = 1.52; 95% CI: 0.49–4.70, p = 0.46, I^2 = 83%) or hospital length of stay (MD = 6.42; 95% CI: -1.42 to 14.26, p = 0.11, I^2 = 84%) between the ketamine and other groups. The high heterogeneity in these analyses suggests that variations in patient populations, sedation protocols, and clinical settings may have influenced the results, requiring cautious interpretation.

As a single-agent sedative, ketamine may present a cost-effective alternative to multi-drug sedation regimens. By providing both sedation and analgesia, ketamine reduces the need for additional analgesics and sedatives, which could lead to lower medication costs, decreased nursing workload, and reduced risk of drug interactions. Additionally, by simplifying sedation protocols, ketamine may offer practical advantages in resource-limited settings, where access to multiple sedative agents is restricted. However, further cost-effectiveness studies are necessary to quantify its economic benefits and assess its impact on hospital resource utilization.

A previous systematic review of ketamine has primarily focused on exploring its effects as an adjunctive agent along with other analgesic and sedation medications (12). However, studying a drug as an adjunctive agent may lead to confounding factors, as the observed outcomes can be influenced by the combined effects of multiple drugs. Recognizing this research gap, our study aimed to address this limitation by exclusively investigating the use of continuous ketamine infusion as a single sedative agent, focusing solely on ketamine's effects without the influence of other sedation medications, which will provide a more accurate and specific understanding of its benefits and potential side effects.

Consequently, their search strategy, inclusion, and exclusion criteria for studies differed notably from those in our systematic review. However, secondary analyses also observed no difference in mortality or hospital length of stay in the ketamine and other groups. Combined with this previous systematic review, our growing body of literature indicates no significant differences in mortality or hospital length of stay for patients receiving ketamine as a single agent.

Our systematic review is unique in that we attempted to characterize adverse events associated with ketamine infusion as a single agent in critically ill patients. Clinical, methodological, and statistical heterogeneity in the included studies precluded meta-analysis, but the most common adverse events observed were atrial fibrillation, hallucinations, and agitation. These findings will hopefully allow clinicians to make informed decisions about important risks when initiating ketamine infusions for post intubation management in critically ill patients. Additionally, this study helps address a critical gap in the literature by evaluating ketamine as a single-agent sedative in pediatric patients, an area with limited research. Ketamine has been studied for pediatric sedation in the emergency setting, with Soleimanpour et al. demonstrating its safety and effectiveness when combined with midazolam and atropine for procedural sedation (23). Our findings expand on this by assessing ketamine as a single-agent sedative in mechanically ventilated pediatric patients, emphasizing the need for further studies to refine dosing and evaluate long-term safety in critical care settings.

5. Limitations

Our study is not exempt from certain limitations that should be acknowledged and considered. We were able to identify seven studies for systematic review and four appropriate for meta-analysis, with different doses of ketamine used in several studies. As a result, we could not assess for evidence of publication bias. In addition, we observed significant clinical and statistical heterogeneity in both primary and secondary outcomes. Furthermore, the patient populations in the in-

cluded studies were notably different (adult vs. pediatric; admission diagnoses), which likely contributed to the statistical heterogeneity observed. We have attempted to account for these limitations by strictly adhering to accepted standards and criteria for conducting and reporting systematic reviews and meta-analyses.

6. Conclusions

Ketamine is an effective single infusion sedative agent in post intubation management of ventilated patients with no significant difference in hospital mortality and LOS compared with the no-ketamine group. Atrial fibrillation and agitation were the most common adverse effects of ketamine. Future research is warranted to better understand appropriate dosing and adverse events as a single sedation agent and which patient populations are most likely to benefit from its use.

7. Declarations

7.1. Acknowledgments

We thank the medical library staff for their support in developing the search strategy.

7.2. Authors' contributions

All authors contributed to the study design, data collection, analysis, and manuscript writing. All authors reviewed and approved the final manuscript.

7.3. Conflict of interest

None of the authors have any actual or potential conflicts of interest to disclose.

7.4. Availability of Data

All data generated or analyzed during this study are included in this published article and its supplementary materials.

7.5. Funding

The authors received no financial support for this article's research, authorship, and/or publication.

7.6. Using artificial intelligence chatbots

Artificial intelligence chatbots were not used in data analysis or interpretation.

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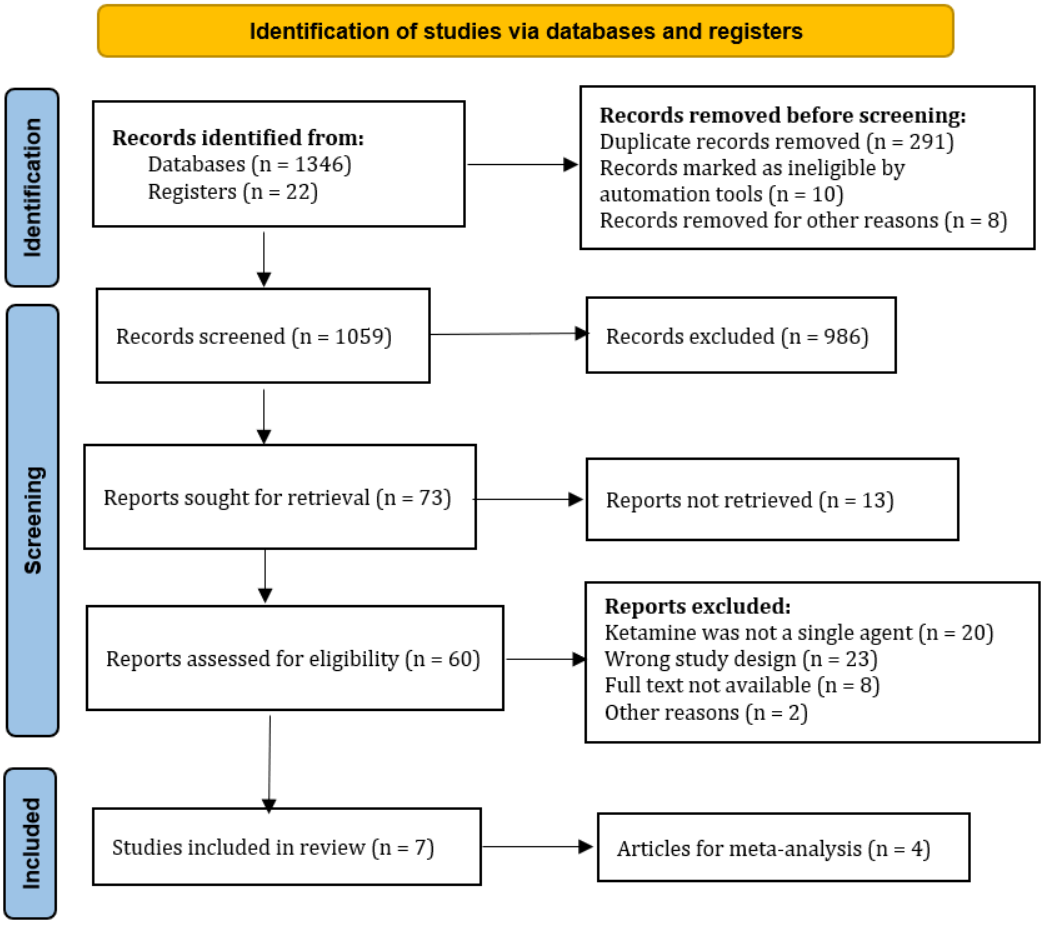

Figure 1: PRISMA 2020 flowchart for new systematic reviews, including sole database and register searches.

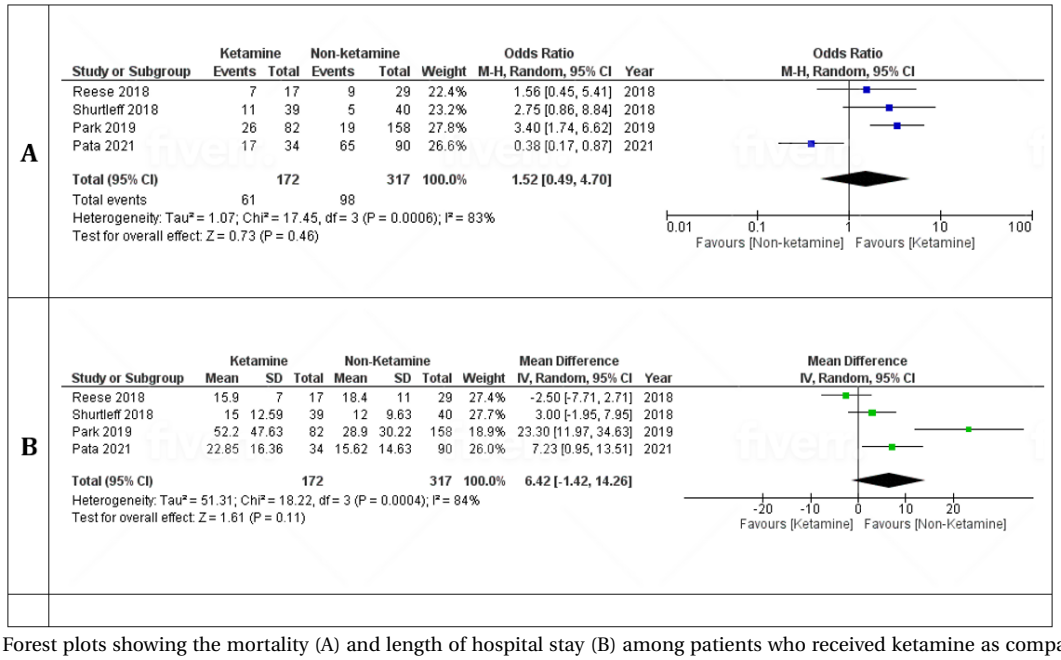

Figure 2: Forest plots showing the mortality (A) and length of hospital stay (B) among patients who received ketamine as compared to the other group.

M-H: Mantel–Haenszel method; IV: Inverse Variance method; SD: Standard Deviation; CI: Confidence Interval; OR: Odds Ratio; df: degrees of freedom; Tau²: between-study variance; Chi²: Cochran's Q statistic; I²: percentage of variation due to heterogeneity; Z: overall effect statistic; SE: Standard Error.

Table 1: Basic characteristics of selected studies (continue)

Reference	Type of study	Indication	Age group	Ketamine and dose	Other agents	Duration	Results and Complications or side effects	Used in quantitative analysis?	Other Notes
Youssef-Ahmed et al., 1996	Cohort study	Severe Bronchospasm	5 months to 17 years	IV bolus 2 mg/kg followed by continuous infusions of 20-60 ug/kg/min	Midazolam and Diazepam	24 hours	The PaO2/FIO 2 ratio increased significantly at 1, 8, and 24 hrs from baseline after ketamine infusion. Increased airway secretions and hallucinations were reported as adverse effects in two patients.	No	Dynamic compliance increased significantly at 1, 8, and 24 hours from baseline after ketamine infusion. Ketamine appears to have few adverse effects that are readily controlled.
Sohaib Khatib et al. 2022	retrospectiveCohort study	Hemodynamic Effects of Ketamine Infusion in the Intensive Care Unit for Maintenance Sedation	The mean age is 47 years	0.94 ± 0.62 mg/kg/h	Propofol and Midazolam	january 2015 and April 2020	continuous ketamine infusion did not reveal a statistically significant favorable hemodynamic effect compared with propofol and midazolam because of the small sample size.	No	Study did not investigate certain clinical factors that could potentially influence the hemodynamic effects of sedative medications. These factors include the duration of ICU stay, concurrent medication use, and the impact of other medical comorbidities.
Umunna et al., 2015	Cohort study	Sedation using ketamine infusion for greater than 24 hours.	>18 years of age	2.0 ± 0.98 mg/kg/hr	Fentanyl	Sep 2011-March 2012	Ketamine seems to have a comparable rate of adverse effects as more commonly used sedatives when used for extended mechanical breathing. Atrial fibrillation and agitation were reported as adverse effects by some patients.	No	ketamine has a favorable safety profile in Sepsis, Acute lung injury, COPD, Asthma, Hemorrhage, and others without significant effects on hemodynamics and agitation
Shurtleff et al., 2018	Cohort study	Patients on mechanical ventilation in the ICU who are sedated with ketamine or non-ketamine medications	Adult patients	5 mg/kg/min	Propofol and dexmedetomidine	Nov 2015 - April 2017	Delirium occurred in 74% of patients with ketamine and 85% of patients with non-ketamine sedatives, and it was insignificant. Coma occurred significantly more in the ketamine group.	Yes	Delirium- and coma-free days were similar in ketamine vs. non-ketamine sedatives. Additionally, patients using ketamine were more likely to be on vasopressor and inotrope support.
Reese et al., 2018	Cohort study	Septic shock requiring mechanical ventilation	18–89 years of age	1–2 mg/kg IV bolus followed by a continuous infusion of 5 mcg/kg/min, titrated to 2 mcg/kg/min every 30 minutes.	Fentanyl, lorazepam, midazolam, and dexmedetomidine.	Phase 2: Jan 2012 - April 2015	A decrease was seen in norepinephrine and vasopressin use in the ketamine group compared to the control group. At 36 hours, one patient experienced a single adverse event, significant agitation, and ketamine was later stopped.	Yes	The use of fentanyl as an analgesic was less in the study group.

Table 1: Basic characteristics of selected studies

Reference	Type of study	Indication	Age group	Ketamine and dose	Other agents	Duration	Results and Complications or side effects	Used in quantitative analysis?	Other Notes
Ramakanth Pata et al., 2021	Cohort study	severe ARDS	18-90 Years of age	Intravenous bolus of 0.5 mg/kg followed by 0.5 mg/kg/hr continuous infusion.	propofol and midazolam	February 2020 to November 2020	Ketamine was found to be a safe sedative in COVID-19 individuals with severe ARDS and was related with a decrease in mortality. Although patients who got ketamine had a longer hospital stay, they had a comparable complication profile to those who did not receive ketamine, including delirium, infectious problems, and acute renal damage. The ketamine group stayed in the hospital for 22.85 days (± 16.36), while the non-ketamine group stayed for 15.62 days (± 14.63) ($p < 0.02$).	Yes	Ketamine's anti-inflammatory properties may not always imply immunosuppression.
Park et al., 2019	Cohort study	critically ill children	Age, median year (IQR), 2.1 (0.7, 5.9)	The median rate of infusion was 8.1 micrograms per kilogram per minute, and the median period of continuous infusion was 6 days	Fentanyl, Midazolam, Dexmedetomidine	January 2015 to December 2017	Continuous ketamine did not cause hemodynamic instability in PICU. Dexmedetomidine was more often administered in the ketamine group than sedatives. Ketamine group had a longer stay in the hospital prior to ICU admission, a longer duration of MV, and a longer stay in the ICU. Ketamine aided in the reduction of cardiac and respiratory rates.	Yes	The ketamine group's high death rate was not due to ketamine. Ketamine was not shown to be a major risk factor for increased death.

IV = Intravenous; PaO/FiO = Partial pressure of arterial oxygen to fraction of inspired oxygen; ICU = Intensive Care Unit; ARDS = Acute Respiratory Distress Syndrome; COPD = Chronic Obstructive Pulmonary Disease; MV = Mechanical Ventilation; PICU = Pediatric Intensive Care Unit; IQR = Interquartile Range.

Appendix 1: Search strategy foe different databases

Database	Strategy
Scopus	TITLE-ABS-KEY ("ketamine infusion" AND "mechanically ventilated" AND ("critical care" OR "intensive care" OR ICU) AND ("post-intubation" OR "post intubation"))
Medline	("Ketamine"[Mesh] OR ketamine[tiab]) AND ("Infusions, Intravenous"[Mesh] OR infusion[tiab]) AND ("Critical Illness"[Mesh] OR "Intensive Care Units"[Mesh] OR ICU[tiab]) AND ("Intubation, Intratracheal"[Mesh] OR "post intubation"[tiab])
ISI	TS=("ketamine infusion" AND "mechanically ventilated" AND ("critical care" OR "intensive care" OR ICU) AND ("post-intubation" OR "post intubation"))

Table 2: Quality assessment using the New Ottawa scale

Studies	Selection (Max 4)				Comparability (Max 2)	Outcome (Max 3)			Total score
	1	2	3	4	5	6	7	8	
Youssef-Ahmed 1996	1	1	1	1	2	1	1	1	9
Sohaib Khatib 2022	1	1	1	1	1	1	1	1	8
Umunna 2015	1	1	1	1	1	1	1	1	8
Shurtleff 2018	1	1	1	1	2	1	1	1	9
Reese 2018	1	1	1	1	2	1	1	1	9
Ramakanth Pata et al., 2021	1	1	1	1	1	1	1	1	8
Park et al., 2019	1	1	1	1	2	1	1	1	9

1. Representativeness of the Exposed Cohort
2. Selection of the Non-Exposed Cohort
3. Ascertainment of Exposure
4. Demonstration That Outcome of Interest Was Not Present at Start of Study
5. Comparability of Cohorts on the Basis of the Design or Analysis
6. Assessment of Outcome
7. Was Follow-Up Long Enough for Outcomes to Occur
8. Adequacy of Follow Up of Cohorts