sciendo Online ahead-of-print. Page numbers NOT for citation purposes. RESEARCH ARTICLE

DOI: 10.2478/jccm-2026-0011

Inhaled sevoflurane in critically ill COVID-19 patients: A retrospective cohort study

Jose J. Zaragoza[1], Marco A. Baez-Garcia[2,3], Jose M. Lomeli-Teran[2,4], Daniela Anzures-Diaz[2], Paola Zamudio-Cantellano[2,4], Job H. Rodriguez-Guillen[2,4]

[1] Hospital H+ Queretaro, Santiago de Querétaro, Mexico
[2] Critical Care Department, Hospital H+ Queretaro, Queretaro, Mexico
[3] Universidad Anahuac Queretaro, Queretaro, Mexico
[4] Colegio Mexicano de Medicina Crítica, Benito Juárez, Mexico

Abstract

Background: Managing sedation in critically ill COVID-19 patients is challenging due to high sedative requirements and organ dysfunction that alters drug metabolism. Inhaled sevoflurane offers a lung-eliminated alternative that may mitigate drug accumulation.

Methods: This single-center, retrospective cohort study analyzed 43 mechanically ventilated COVID-19 patients (March–November 2020). Patients received inhaled sevoflurane adjunctive to IV sedation (n=30) or IV sedation alone (n=13). The primary outcome was the cumulative dose of IV sedatives over 7 days. Secondary outcomes included time to extubation and antipsychotic use.

Results: There was no significant difference in the cumulative dose of IV sedatives between groups. However, the sevoflurane group had a significantly longer median duration of mechanical ventilation (206 [IQR 144-356] vs 144 [IQR 115-156] hours, p=0.005) and a higher requirement for antipsychotic medication (66.6% vs 15.3%, OR 18.6, p=0.011). Daily doses of propofol were lower in the sevoflurane group on specific days, but overall burden was unchanged.

Conclusions: In this cohort, adjunctive inhaled sevoflurane did not significantly reduce the cumulative burden of IV sedatives and was associated with delayed extubation and increased antipsychotic use. While sevoflurane is a feasible alternative, these findings suggest caution regarding weaning and delirium management in COVID-19 patients.

Keywords: COVID-19, sevoflurane, sedation, mechanical ventilation, intensive care unit, delirium

Trial registration: Clinicaltrials.gov (NCT06208592)

Received: 11 April 2025 / Accepted: 16 January 2026

Introduction

The COVID-19 pandemic has posed an unprecedented challenge to healthcare systems worldwide. In Mexico, the impact has been particularly significant, with a high burden of hospitalizations and mortality. The burden of hospitalizations and mortality due to COVID-19 in Mexico has been significant, as detailed in several studies. From March 2020 to March 2022, Mexico experienced four epidemic waves, with 5,702,143 confirmed cases, of which 680,063 (11.9%) were hospitalized, and 324,436 (5.7%) died [1].

Managing critically ill COVID-19 patients in the intensive care unit (ICU), especially those requiring invasive mechanical ventilation, has been particularly demanding. In a tertiary care center in Mexico City, in-hospital mortality for severe COVID-19 was 30.1%, with overcrowding and lack of ICU beds contributing significantly to mortality rates [2] The need for mechanical ventilation was a critical predictor of mortality, increasing the odds of death substantially [3].

Sedation is crucial for patients undergoing mechanical ventilation to ensure tolerance of the ventilator and minimize discomfort [4,5]. However, conventional intravenous (IV) sedation is associated with several drawbacks, including hemodynamic instability, prolonged sedation, delirium, and delayed awakening [5,6]. Drug accumulation in critically ill COVID-19

* Correspondence to: Jose J. Zaragoza, Hospital H+ Queretaro, Santiago de Querétaro, Mexico. Email: zaragozagalvan@hotmail.com

patients is a complex issue, primarily driven by altered pharmacokinetics resulting from hepatic and renal impairment associated with the disease [7,8]. This accumulation leads to prolonged deep sedation, which hinders weaning from mechanical ventilation and may worsen clinical outcomes [7,8].

Inhaled anesthetics, such as sevoflurane, have emerged as an alternative approach for ICU sedation. Sevoflurane is a widely used volatile anesthetic with a rapid onset of action, easy titration, and a favorable safety profile [9]. Its primary route of elimination is through the lungs, making it particularly attractive for patients with multi-organ dysfunction [6]. Moreover, recent studies suggest that sevoflurane may have anti-inflammatory and lung-protective properties, which could be beneficial in the context of COVID-19 [10]. Other studies in the context of ARDS suggested that sevoflurane might offer benefits over benzodiazepines in terms of improved oxygenation and reduced oxidative stress in the lung, although no significant differences were observed in terms of hospital stay or mechanical ventilation-associated pulmonary damage [11,12]

This study investigated the use of inhaled sevoflurane as an adjunctive therapy for COVID-19 patients receiving invasive mechanical ventilation. The primary objective of this study was to compare the dosage of IV sedatives required for sedation, analgesia, or muscle relaxation in patients receiving inhaled sevoflurane versus those receiving conventional IV sedation. Secondary objectives included comparing the duration of mechanical ventilation, ICU length of stay, time to awakening, need for reintubation, incidence of delirium, and use of antipsychotics. We hypothesized that sevoflurane would reduce the need for IV conventional sedatives and potentially mitigate the adverse effects associated with these agents.

Given the scarcity of data on sevoflurane specifically in the COVID-19 population, this study aims to evaluate its impact not only on sedative consumption but also on critical patient-centered outcomes like extubation time and delirium surrogates.

Methods

Design and setting

This was a single-center, retrospective, observational cohort study conducted in the COVID-19 ICU of a tertiary care teaching hospital in Queretaro, Mexico from March 1st to November 20th, 2020. During the sanitary emergency an area for COVID patients was created where both critical and semi-critical acute patients were attended as a respiratory-ICU. The protocol was registered at clinicaltrials.gov (NCT06208592). The study was approved by the Institutional Review Board of Hospital H+ Queretaro (approval number: CEI2020a-02V1).

Participants

All consecutive adult patients (≥18 years old) patients admitted to the respiratory ICU with confirmed SARS-CoV-2 infection during the study period were screened for eligibility. Those requiring invasive mechanical ventilation were included in the study. Exclusion criteria were patients with a known allergy to sevoflurane, those who died within 24 hours of admission, and those transferred to another hospital before extubation. In this retrospective cohort study, allocation to the sevoflurane or control group was determined by the attending physician's clinical judgment and the availability of anesthesia conserving devices (AnaConDa) during the pandemic, rather than randomization. Sedation depth was monitored by nursing and medical staff using the Richmond Agitation-Sedation Scale (RASS), targeting a level of -2 to -4 during the acute phase of mechanical ventilation, though strict adherence was variable due to pandemic conditions.

Data Collection and Outcomes

Baseline demographic and clinical data were collected from medical records. This included age, sex, comorbidities, laboratory values (e.g., lactate, calcium, procalcitonin), and severity of illness scores (e.g., SOFA score). The primary outcome was the cumulative dose of IV sedatives (propofol, dexmedetomidine, and opioids) administered during the first 7 days. Secondary outcomes included duration of mechanical ventilation and time to successful extubation (represented as the period since initiation of spontaneous breathing trials and successful mechanical ventilation weaning), incidence of delirium assessed using the Confusion Assessment Method for the ICU[13] (CAM-ICU) and indirectly by the prescription of antipsychotics (haloperidol, olanzapine, quetiapine, and risperidone), time to awakening (defined as), need for reintubation, and incidence of ventilator-associated pneumonia confirmed by positive sputum culture.

calcium (8.6 [8.3-8.9] *vs* 8.1 [7.6-8.5]; p=0.003), higher procalcitonin (0.4 [0.17-1.17] *vs* 0.105 [0.05-0.36] p=0.003) and a lower average propofol dose on day one (1.92 [1.79-2.37] *vs* 1.48 [1.05-1.93], p= 0.001. Other relevant variables such as comorbidities, severity of illness scores or crucial laboratory values were not different among groups. All patient baseline characteristics are depicted in Table 1.

Table 1. Baseline clinical characteristics of patients according to sevoflurane use

Variable	Controls (n= 13)	Sevoflurane (n=30)	Total (n=43)	p value
Demographic characteristics				
Age (years)	46 (40-61)	54 (48-60)	53 (45-61)	0.277
Male sex (%)	11 (84.6)	26 (86.6)	37 (86.0)	1.000
Weight (kg)	83 (75-92)	85 (75-95)	85 (75-95)	0.760
Height (m)	166 (162-175)	172 (165-177)	171 (163-177)	0.307
Systemic Hypertension (%)	4 (30.7)	8 (26.6)	12 (27.9)	1.000
Diabetes Mellitus (%)	3 (23)	10 (33.3)	13 (30.2)	0.720
Obesity (%)	7 (53.8)	16 (53.3)	23 (53.4)	1.000
COPD (%)	0	1 (3.3)	1 (2.3)	1.000
Asthma (%)	0	2 (6.6)	2 (4.6)	1.000
Sleep apnea obstructive syndrome (%)	1 (7.6)	2 (6.6)	3 (6.9)	1.000
Smoking (%)	0 (0)	1 (3.3)	1 (2.3)	1.000
Hypothyroidism (%)	2 (15.3)	0 (0)	2 (4.6)	0.086
Immunodeficiencies (%)	2 (15.3)	1 (3.3)	3 (6.9)	0.213
Hematology (%)	2 (15.3)	2 (6.6)	4 (9.3)	0.572
Chronic Heart Failure (%)	1 (7.6)	1 (3.3)	2 (4.6)	0.518
CORADS 6 (%)	2 (15.3)	10 (33.3)	12 (27.9)	0.290
Total SOFA	6 (5-7)	6 (5-7)	6 (5-7)	0.805
Respiratory SOFA	3 (2-3)	3 (3-3)	3 (3-3)	0.433
CV SOFA	3 (3-4)	3 (3-3)	3 (3-3)	0.405
Renal SOFA	0 (0-0)	0 (0-0)	0 (0-0)	0.344
Hematological SOFA	0 (0-0)	0 (0-0)	0 (0-0)	0.029*
Hepatic SOFA	0 (0-0)	0 (0-0)	0 (0-0)	0.172
Sevoflurane dose	N/A	10 (9.3-10)	10 (9.3-10)	N/A
Sevoflurane use day 1 (%)	N/A	20 (66.6%)	20 (46.5%)	0.000*
Day of symptoms at admission	9 (7-12)	9 (7-12)	9 (7-12)	0.968
Day of symptoms at intubation	12 (9-14)	9 (8-12)	10 (8-14)	0.143
Heart Rate				
Maximum	92 (80-100)	84 (80-93)	85 (80-96)	0.404
Minimum	62 (55-71)	57 (50-63)	58 (52-65)	0.177
Mean Arterial Pressure				
Maximum	95 (90-97)	94 (90-103)	95 (90-99)	0.915
Minimum	72 (70-74)	70 (68-73)	71 (68-74)	0.482
Maximum lactate at day one (mmol/L)	1.4 (1.3-1.6)	1.9 (1.6-2.3)	1.7 (1.4-2.3)	0.023*
PEEP maximum day 1	10 (9-12)	12 (10-12)	12 (10-12)	0.122
PaO_2 / FiO_2	149 (126-204)	156 (124-192)	151 (124-199)	0.801
Urinary flow (mL)	1442 (980-1890)	1652 (950-2130)	1630 (950-2130)	0.894
Hemoglobin (g/dL)	14.1 (12.8-15.4)	15.7 (14.1-16.6)	14.9 (13.9-16.5)	0.095
Leucocytes (× 10^9/L)	7.15 (6.43-14.7)	11.9 (9.1-13.7)	11.6 (7.15-13.7)	0.272
Neutrophiles (× 10^9/L)	5.48 (5.06-11.7)	10.2 (6.93-11.7)	9.53 (5.79-11.7)	0.095
Lymphocytes (× 10^9/L)	.75 (.6- .94)	.99 (.74 – 1.25)	.91 (.62 – 1.23)	0.109
Platelets (× 10^9/L)	223 (195-340)	233 (206-312)	233 (195-317)	0.926
Creatinine (mg/dL)	0.9 (0.6- 1.1)	0.7 (0.7- 0.8)	0.8 (0.7- 0.9)	0.501
BUN (mg/dL)	19 (14-24)	16 (12-21)	16 (13-23)	0.499
Sodium (mEq/L)	139 (137-141)	140 (138-142)	140 (137-142)	0.154
Potassium (mEq/L)	4.1 (3.8-4.2)	4.3 (3.9-4.7)	4.1 (3.8- 4.6)	0.217

(Continued on page 5)

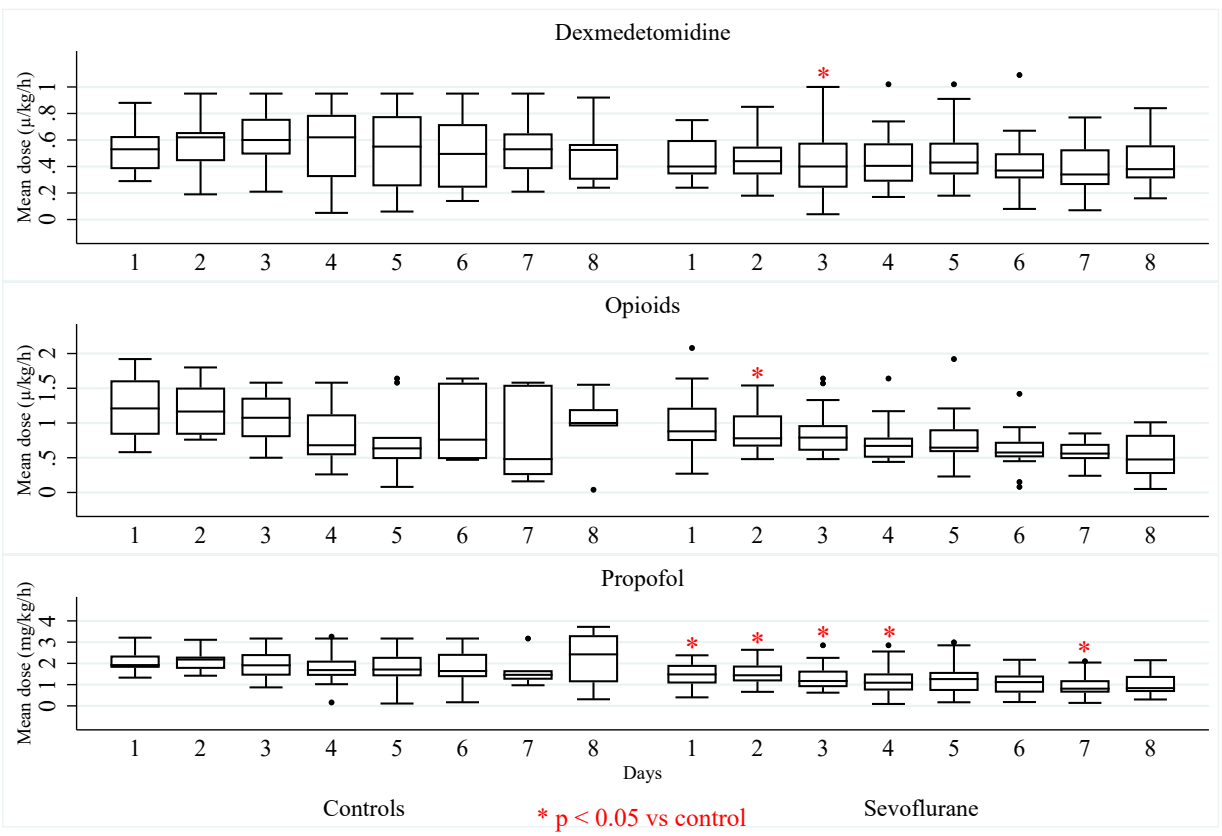

Fig. 2. Box plot of mean daily dosage of sedatives by group in the first 7 days of follow up.

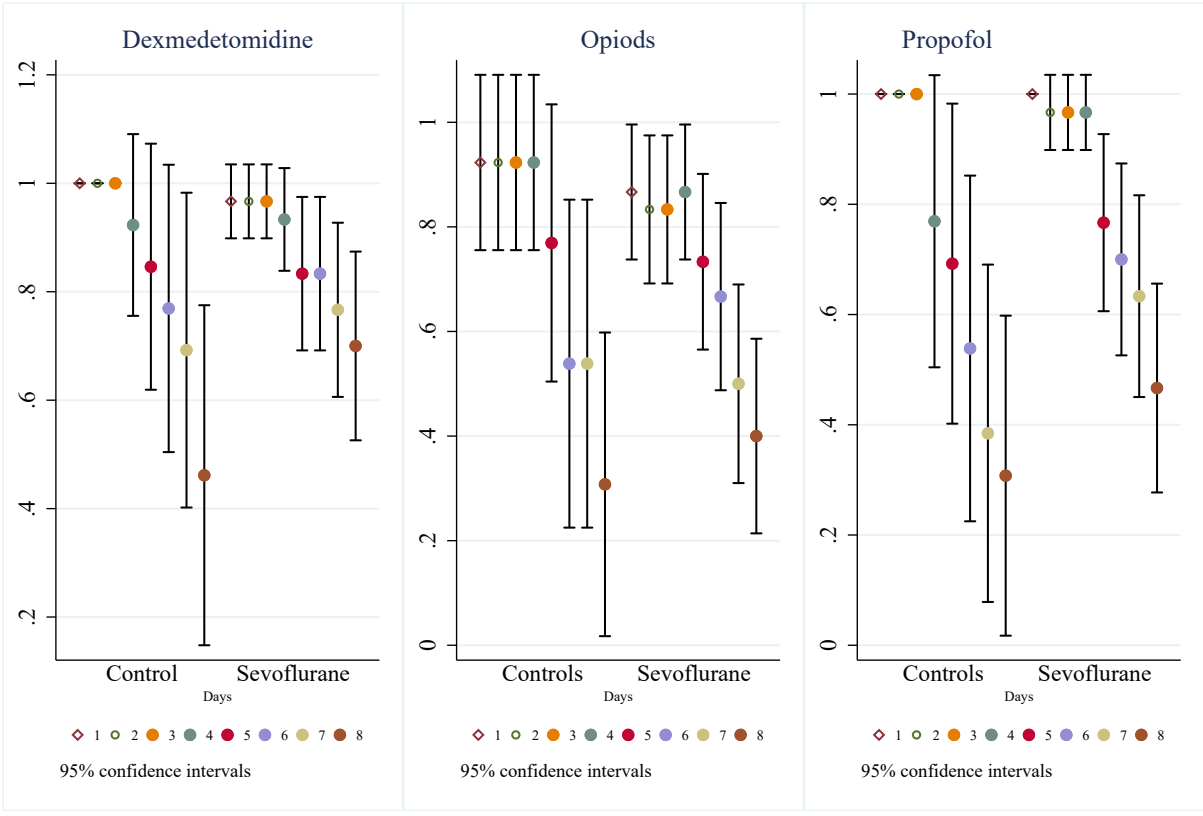

Fig. 3. 95% Confidence Interval plot of proportion of patients on every main sedative per day by group.

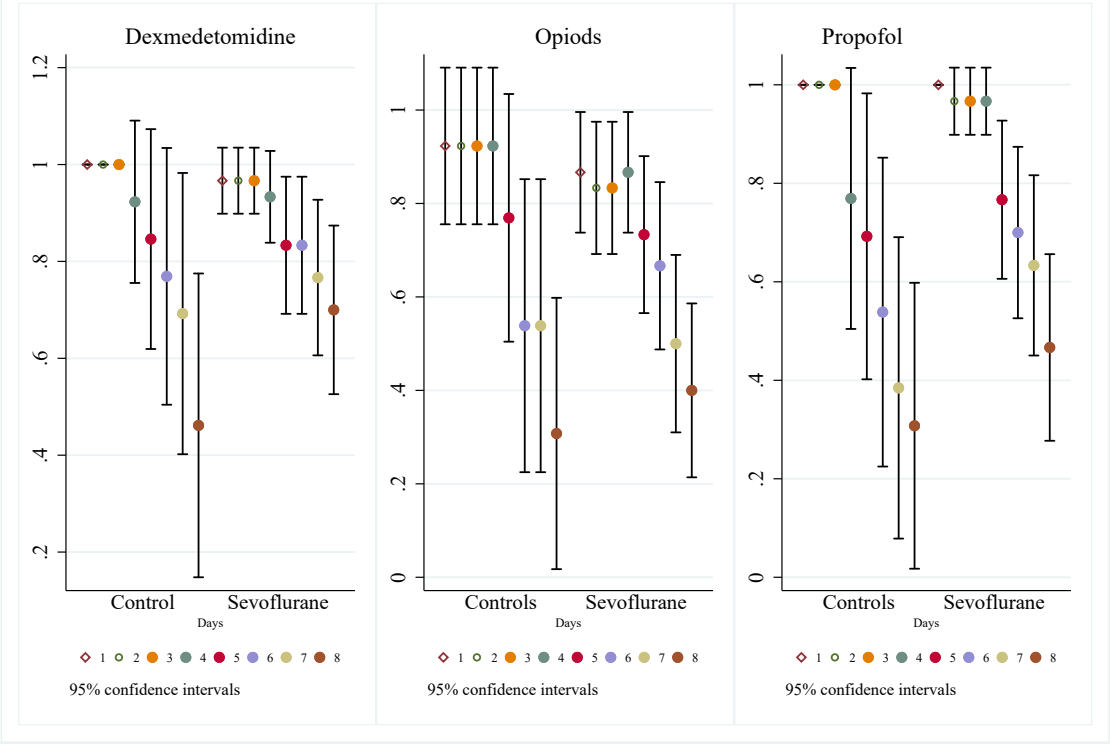

Fig. 4. Partial-regression leverage plots or adjusted partial residual plots for primary outcome variables.

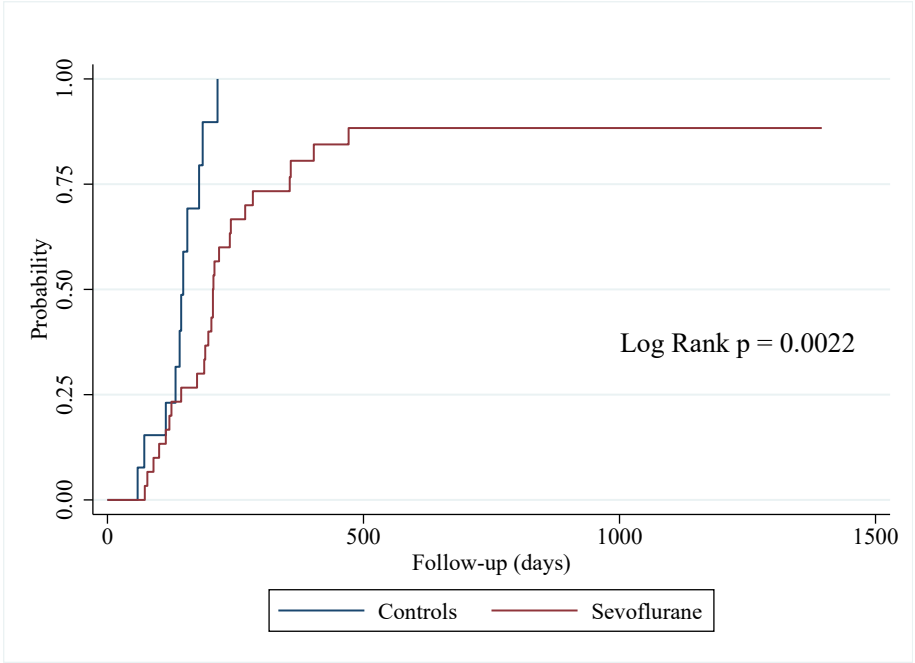

Fig. 5. Kaplan-Meier estimates of probability of successful extubation.

ble. Multiple logistic regression analysis was performed to assess the association between sevoflurane use and the need for antipsychotic medication, adjusting for the same covariates as in the primary analysis, results are presented in Table 4. Sevoflurane use was independently associated with an increased risk of requiring antipsychotic medication (OR 18.682, [95% CI 1.965-177.5], p=0.011). No other covariate was independently associated with an increased risk of reintubation or ventilator-associated pneumonia. No serious adverse events related to sevoflurane administration were observed.

patients with severe sepsis and ARDS, the efficiency of gas exchange is compromised, potentially leading to unpredictable serum concentrations of sevoflurane compared to patients with healthy lungs, similar to other patients [26,27]. This pharmacokinetic variability might explain the prolonged time to extubation observed in our sevoflurane group, as elimination of the gas could be delayed in consolidated lung tissue, leading to a 'wash-out' period longer than anticipated.

Strengths and limitations

Our study possesses several strengths. First, it provides granular, day-by-day data on sedative consumption in a real-world setting during the peak of the COVID-19 pandemic, reflecting actual clinical practice under severe resource constraints. Second, unlike studies focusing solely on drug costs or depth of sedation, we analyzed critical patient-centered outcomes, identifying crucial safety signals regarding extubation latency and delirium surrogates (antipsychotic use) that are clinically relevant for long-term ICU recovery.

However, several limitations must be acknowledged. First, the sample size was small (n=43) and unbalanced, with a limited number of control patients (n=13). This reduces the statistical power of our analysis and increases the risk of type II errors, potentially masking smaller benefits of the intervention regarding cumulative doses. Second, the single-center, retrospective design inherently introduces selection bias; allocation to the sevoflurane group was determined by device availability and clinician preference rather than randomization. Although we used multivariate regression to adjust for baseline severity confounders (e.g., SOFA score, lactate, calcium), residual confounding cannot be ruled out.

Third, while the clinical target was light-to-moderate sedation (RASS -2 to -4), the overwhelming pandemic environment precluded strict adherence to standardized sedation protocols or daily sedation interruption trials. Consequently, variations in sedation depth management between attending physicians could have influenced the time to extubation. Fourth, we lacked granular longitudinal data on the severity of sepsis or daily lung mechanics for all patients, limiting our ability to fully correlate pharmacokinetic alterations with specific degrees of alveolar-capillary damage. Finally, as an observational study, our findings establish an association but cannot prove causality between sevoflurane use and the observed delay in extubation.

Conclusions

In this study, the use of inhaled sevoflurane as an adjunctive sedative in critically ill COVID-19 patients did not significantly reduce the cumulative dose of intravenous sedatives over the first week of ventilation, although transient reductions in daily propofol requirements were observed.

Crucially, sevoflurane use was associated with a longer time to successful extubation and an increased risk of requiring antipsychotic medication. These findings suggest that while sevoflurane is a viable alternative during sedative shortages, it requires careful monitoring of sedation depth and may present challenges during the weaning process in patients with severe respiratory failure.

Further randomized controlled trials are warranted to clarify the pharmacokinetic impact of severe lung injury on volatile anesthetics and to validate their safety profile regarding long-term neurocognitive outcomes.

Authors' contributions

...

...

...

...

Conflict of interest

None to declare.

References

1. Loza A, Wong-Chew RM, Jimenez-Corona M-E, et al. Two-year follow-up of the COVID-19 pandemic in Mexico. Front Public Health. 2022;10:1050673.
2. Olivas-Martinez A, Cardenas-Fragoso JL, Jimenez JV, et al. In-hospital mortality from severe COVID-19 in a tertiary care center in Mexico City; causes of death, risk factors and the impact of hospital saturation. PLoS One. 2021;16(2):e0245772.
3. Cortes-Telles A, Figueroa-Hurtado E, Ortiz-Farias DL, et al. Modeling mortality risk in patients with severe COVID-19 from Mexico. Front Med (Lausanne). 2023;10:1187288.
4. Kim H, Lee J, Kim H, et al. Volatile sedation in the intensive care unit: A systematic review and meta-analysis. Medicine [Internet]. 2017 [cited 2021 Aug 17];96(49).
5. Jerath A, Panckhurst J, Parotto M, et al. Safety and Efficacy of Volatile Anesthetic Agents Compared With Standard Intravenous Midazolam/Propofol Sedation in Ventilated Critical