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Original article

SEDATION WITH INHALED SEVOFLURANE IN THE INTENSIVE CARE UNIT

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Abstract

Introduction: Critically ill patients often develop the Post-Intensive Care Syndrome (PICS). Current sedation guidelines mainly rely on intravenous agents. Inhaled sedatives are a promising alternative with favorable pharmacokinetics and potential benefits in critical care settings. However, their application in Latin America remains unexplored.

Methods: Case-series study that included adult ICU patients who underwent deep sedation with sevoflurane using the SEDANA anesthetic conserving device. Data on demographics, sedation protocols, adverse events, and outcomes were collected. Statistical analysis assessed changes over time in laboratory parameters.

Results: Eleven patients were included, with sevoflurane administered via artificial airways. Inhaled sedation led to the successful cease of intravenous sedatives in 10 of 11 patients, and reduction of at least 30% in opioid dose. No significant adverse effects were observed. Barriers to adherence included device-related issues and challenges in healthcare staff training.

Conclusion: Sevoflurane effectively achieved sedation goals in ICU patients, reducing the need for additional sedatives and opioids. Our findings support the safety and efficacy of inhaled sedatives in ICU settings and highlight the importance of further research in this area. Longer-term studies are needed to fully determine the impact of inhaled sedatives in ICU patients.

Key words: inhaled sedation, sevoflurane, intensive care unit, critical care, intravenous sedation, post-intensive care syndrome

Resumen

Sedación inhalada con sevoflurano en la unidad de cuidados intensivos

Introducción: Los pacientes críticamente enfermos a menudo desarrollan el Síndrome Post-Cuidados Intensivos (PICS). Las pautas actuales de sedación se basan principalmente en agentes intravenosos. Los sedantes inhalados son una alternativa prometedora con farmacocinética favorable y beneficios potenciales en entornos de cuidados críticos. Sin embargo, su aplicación en América Latina sigue sin explorarse.

Métodos: Estudio de serie de casos que incluyó a pacientes adultos de UCI que recibieron sedación profunda con sevoflurano utilizando el dispositivo conservador anestésico SEDANA. Se recopilaron datos demográficos, protocolos de sedación, eventos adversos y resultados. El análisis estadístico evaluó los cambios en el tiempo en los parámetros de laboratorio.

Resultados: Se incluyeron once pacientes, a quienes se les administró sevoflurano a través de vías respiratorias artificiales. Se incluyeron once pacientes, a quienes se les administró sevoflurano a través de vías respiratorias artificiales. La sedación inhalada llevó a la cesación exitosa de sedantes intravenosos en 10 de los 11 pacientes, con una reducción de al menos 30% la dosis de opioides. No se observaron efectos adversos significativos. Las barreras para la adherencia incluyeron problemas relacionados con el dispositivo y desafíos en la capacitación del personal de salud.

Conclusión: El sevoflurano logró de manera efectiva los objetivos de sedación en pacientes de UCI, reduciendo la necesidad de sedantes y opioides adicionales. Nuestros hallazgos respaldan la seguridad y eficacia de los sedantes inhalados en entornos de UCI y resaltan la importancia de una mayor investigación en esta área. Se necesitan estudios a más largo plazo para determinar completamente el impacto de los sedantes inhalados en pacientes de UCI.

Palabras clave: sedación inhalada, sevoflurano, unidad de cuidados intensivos, cuidados críticos, sedación intravenosa, síndrome post-cuidados intensivos

KEY POINTS

- The study observed that inhaled sevoflurane in ICU patients successfully replaced intravenous sedatives, reducing the use of opioids.
- No significant adverse effects were observed with the use of inhaled sevoflurane, indicating its safety profile in ICU settings.
- Device issues and challenges in healthcare personnel training were identified as barriers to the adoption of inhaled sedation in the ICU, highlighting the need to address these obstacles for broader and more effective usage.

Critically ill patients often experience negative consequences following their admission to the Intensive Care Unit (ICU). Ineffectively management of pain, excessive sedation, the onset of delirium, prolonged immobility, and social isolation are risk factors for the development of ICU acquired weakness, motor disability, and cognitive impairment, leading to Post-Intensive Care Syndrome[1,2].

Current sedation guidelines and consensus, periodically updated, primarily rely on intravenous agents[3–5]. However, intravenous sedation may entail adverse effects such as accumulation, tolerance, withdrawal, delirium, and hemodynamic instability[6-9]. Inhaled sedative agents commonly used in general anesthesia are valid alternatives due to their favorable pharmacokinetics, including rapid respiratory elimination, limited hepatic metabolism, and no accumulation[10]. Furthermore, their cardioprotective effects has been studied in the perioperative period of cardiovascular surgeries[11,12], as well as their utility in neurocritical patients for rapid neurological examination[13,14]. Inhaled sedation in the context of critical illness has the potential to reduce sedatives-related adverse events and improve outcomes compared to intravenous sedation[15,16].

To date, there is no information regarding the application of inhaled sedation in Latin America within the ICU context. The aim of this study is to describe the clinical characteristics and clinical outcomes of patients undergoing inhaled sedation, explore whether there is an association between the use of inhaled sedatives and the reduction of intravenous sedatives and analgesics, while also identifying and examining the barriers to adherence to its use.

Materials and methods

A case-series study was conducted from January of 2022 until December of 2023 in the ICU of two high-complexity university hospitals in Argentina. We performed a consecutive sampling strategy; therefore, all adult patients who underwent deep sedation with inhaled sedatives during the ICU stay were included.

Inhaled sedation was delivered using the Sedaconda anesthetic conserving device (SEDANA Medical, Danderyd, Sweden). The volatile agent administered was sevoflurane. In all cases, sedoanalgesia was applied according to the recommendations of the Pain, Agitation/sedation, Delirium, Immobility, and Sleep (PADIS) guidelines, following the A-F bundle approach[3,17]. In all cases, a target of deep sedation was pursued, defined as -4 or -5 on the Richmond Agitation Sedation Scale (RASS), as documented in the electronic medical records. To assess whether the objectives were achieved, the nursing team systematically measured patients' RASS four times a day, and additionally conducted reassessments in response to clinical changes.

Sevoflurane was administered according to age-adjusted minimal alveolar concentration to achieve steady-state end-tidal sevoflurane concentrations targets of 0.5 to 1%, monitored through a gas analyzer (SEDANA Medical, Danderyd, Sweden), with concomitant processed electroencephalogram-based monitoring[18].

This study was approved by the institutional ethics committees. Our article complies with the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines for observational cohort studies[19] (Supplementary material). Informed consent was obtained from the participants.

Variables and outcomes

Demographic variables such as age, sex, ICU severity scores, comorbidities, and in-hospital mortality of the series were registered. With the aim of determining whether there was renal failure, hypernatremia, or elevation of transaminases, laboratory variables such as serum sodium, creatinine, and glutamic oxaloacetic transaminase (GOT) were obtained consecutively during the next 5 days following the initiation of inhaled sedation. Furthermore, serious and potentially lethal adverse effects were closely monitored, such as hypersensitivity/allergy or malignant hyperthermia.

Mechanical ventilation parameters, as well as vasopressors, analgesics, and intravenous sedatives adjusted by weight, were recorded both before initiating inhalation sedation and 6 hours after the start of inhaled sedation administration, when it is presumed that steady state has been reached. The total volume of volatile agents administered, as well as the duration of inhaled sedation, were also registered.

To identify and analyze the barriers to adherence to inhaled sedatives use, attending physicians self-reported potential issues encountered during the circuit assembly and drug delivery. These issues encompassed improper placement of components, assembly configurations lacking validation from the manufacturer, and gas leakage. Additionally, challenges linked to healthcare staff training were documented, including instances of incorrect bolus administration and insufficient knowledge about the syringe pump's management. Finally, complications involving the obstruction of the anesthetic conserving device were also documented.

The number of patients who died or were discharged, and those who stayed in ICU until December 31th of 2023 was recorded. Additionally, ICU length of stay was determined.

Statistical analysis

No statistical sample size calculation was performed in advance and the sample size was equal to the number of patients treated during the study period. Continuous variables were expressed as medians and interquartile ranges or simple ranges, as appropriate. Categorical variables were summarized as counts and percentages. To assess changes over time in laboratory parameters (Creatinine, GOT, and Sodium) between day 1 and day 3, and day 5, the Wilcoxon signed-rank test was employed. This non-parametric test was chosen due to the correlation between observations. All statistical tests were two-tailed, and significance was set at $p<0.05$. All statistical tests were 2-tailed, and statistical significance was defined as $p<.05$. The analysis has not been adjusted for multiple comparisons, and given the possibility of a type I error, the findings should be interpreted as exploratory and descriptive. All the analyses were performed using STATA Software, version 16.

Results

During the study period, a total of 11 patients were included. Ten patients were male with a median age of 44 years (IQR 37-50). The most prevalent comorbidity was hypertension. Demographic characteristics of the patients, including the reason for admission and severity scores, are listed in Table 1.

In all cases, sevoflurane was administered via an artificial airway using the anesthetic conserving device. Nine patients received inhaled sedatives via endotracheal tube, and 2 via tracheostomy tube. Inhaled sedatives were maintained for a median of 2 days (IQR 2-6).

Regarding the use of intravenous sedation, all patients were receiving continuous propofol infusion with a median dose of 1.7 mg/kg/h (IQR 1.5-2.1). After the initiation of sevoflurane, propofol was successfully discontinued in 10 out of 11 patients. Also, five patients were receiving concurrent continuous infusion of midazolam previous to inhaled sedation, with a median dose of 0.27 mg/kg/h (IQR 0.22-0.33). All patients suspended midazolam after the initiation of sevoflurane. Finally, one patient also received dexmedetomidine infusion and successfully discontinued it. The Richmond Agitation-Sedation Scale (RASS) goal was achieved in all patients.

Table 1 | Demographic characteristics of the patients

	Demographics			Severity scores			Intravenous sedation		Inhaled sedation		
	Sex	Age	Reason for admission	SOFA	APACHE II	Charlson	Sedative	Analgesic	Sedative	Analgesic	Days of use
Case 1	♀	51	CAP	1	2	4	Propofol / Midazolam	Fentanyl	Sevoflurane	Fentanyl (80%↓)	2
Case 2	♂	43	Tracheal trauma	1	5	1	Propofol / Dexmedetomidine	Morfine	Sevoflurane	Morfine (67%↓)	5
Case 3	♂	46	Cerebellar hemorrhage	6	17	2	Propofol / Midazolam	Fentanyl	Sevoflurane	Fentanyl (=)	2
Case 4	♂	36	Peritonitis	6	21	2	Propofol / Midazolam	Morfine	Sevoflurane	Morfine (100%↓)	2
Case 5	♂	28	Tracheal resection	0	4	1	Propofol / Midazolam	Morfine	Sevoflurane	Morfine (75%↓)	1
Case 6	♂	37	COVID-19	8	20	3	Propofol / Midazolam	Fentanyl	Sevoflurane	Fentanyl (17%↓)	6
Case 7	♂	59	Fournier's gangrene	4	17	5	Propofol	Fentanyl	Sevoflurane	Fentanyl (40%↓)	3
Case 8	♂	72	CAP	3	8	2	Propofol	Remifentanil	Sevoflurane	Remifentanil (33%↓)	1
Case 9	♂	22	Severe TBI	4	13	0	Propofol	Remifentanil	Sevoflurane	Remifentanil (25%↓)	1
Case 10	♂	49	ARDS	2	10	1	Propofol	Fentanyl	Sevoflurane	Fentanyl (28%↓)	6
Case 11	♂	44	Viral myocarditis	2	7	0	Propofol	Fentanyl	Sevoflurane	Fentanyl (28%↓)	1

SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health disease Classification System II; CAP: community acquired pneumonia; TBI: traumatic brain injury; ARDS: acute respiratory distress syndrome

In terms of analgesia, 2 patients were receiving continuous infusion of morphine with a median dose of 0.03 mg/kg/h (IQR 0.03-0.04), and achieved a dose reduction of 67% and 75%, respectively. Also, 5 were receiving fentanyl, with a median dose of 0.78 mcg/kg/h (IQR 0.67-0.88). The median reduction of fentanyl dose was 34.1% (IQR 25.5-48.5). Three patients used remifentanil with a median dose of 0.18 mcg/kg/min (IQR 0.16-0.18), while the reduction was 33% (median 0.12 IQR 0.11-0.13). There was one patient receiving morphine before the use of inhaled sedation whose analgesic strategy was changed to fentanyl due to acute renal failure at admission. Global percentage of opioid drugs reduction was 33% (IQR 25-80).

We did not observe significant changes regarding hemodynamics. The median dose of norepinephrine was 0.1 mcg/kg/h (IRQ 0.06-0.25) before the onset of sevoflurane and 0.08 mcg/kg/h (IQR 0.06-0.22) afterward.

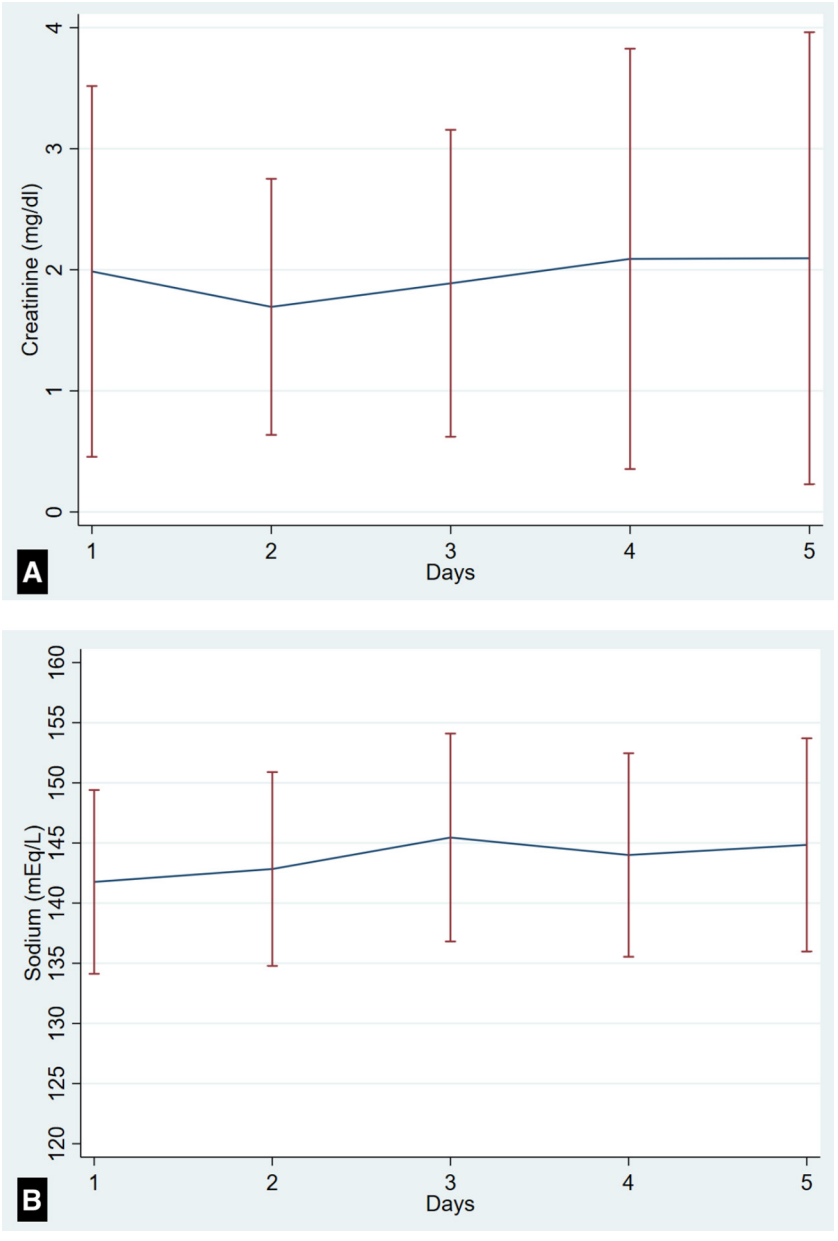
Regarding barriers to adherence, attending physicians reported that four patients presented issues encountered during the circuit assembly and drug delivery. In one patient improper placement of circuit components was configured, one patient received an incorrect bolus without any adverse effect, and in two cases the anesthetic conserving device presented obstruction due to respiratory secretions. Finally, regarding adverse effects, one patient developed hypernatremia, and one experienced an elevation of transaminases, with no patient developing acute renal injury. None of the patients presented serious or potentially lethal adverse effects, such as hypersensitivity/allergy or malignant hyperthermia. Table 2 and Figure 1 illustrates changes over time of laboratory values. The median duration of invasive mechanical ventilation was 25 days (IQR 17-29). Details regarding the mode of mechanical ventilatory assistance are found in the Supplementary material. The median length of hospital stay was 35 days (IQR 24-48), with a median stay in the ICU of 28 days (IQR 25-42). The mortality rate of the series was 20%.

Table 2 | Change over time of laboratory values

Laboratory - median (IQR)	Day 1	Day 3	Day 5	p. Day 1 vs. day 3	Day 1 vs. day 5
Creatinine (mg/dl)	1.74 [0.92;2.13]	1.89 [0.83;2.60]	1.45 [0.78;2.90]	0.53	0.83
Sodium (mEq/L)	140 [137;149]	146 [138;154]	144 [140;151]	0.02	0.03
GOT (mg/dl)	35.0 [18.8;75.8]	25.0 [20.0;53.0]	36.0 [23.0;97.0]	0.3	0.5

IQR: interquartile range; GOT: glutamic oxaloacetic transaminase

Figure 1 | Changes over time of Creatinine (A) and serum Sodium (B) (mean and standard deviation)



Discussion

In this case-series study analyzing 11 patients undergoing deep sedation with inhaled sedatives in ICU, we observed that the use of sevoflurane was effective in achieving sedation goals without any concomitant sedative. Likewise, we noticed a reduction in the use of opioids. Also, sevoflurane presented an appropriate safety profile without evidence of serious associated adverse effects.

Our findings are in accordance with the three primary trials assessing the effectiveness of inhaled sedatives in the ICU conducted to date. In the initial study from 2004, researchers observed that isoflurane inhalation appears to be both safe and efficacious. Notably, it demonstrated shorter wake-up times and a lower risk of accumulation compared to midazolam[20]. In the 2011 trial by Mesnil et al., the investigation revealed that long-term inhaled sevoflurane sedation serves as a secure and effective alternative to intravenous propofol or midazolam. This approach led to reduced wake-up and extubation times, as well as diminished post-extubation morphine consumption, ultimately enhancing the quality of awakening[21]. Finally, Meisner et al. conducted an open-label, phase 3, randomized controlled, non-inferiority trial, establishing that isoflurane, when compared to propofol for up to 54 hours, proved to be effective, non-inferior to propofol, and well-tolerated. Additionally, their observations indicated that wake-up times with isoflurane were shorter than with propofol, with a significantly faster wake-up noted on day 2 at the end of the study treatment. These findings suggest that distinctions in emergence between isoflurane and intravenous sedation may become more pronounced with prolonged exposure, particularly beyond 24 hours, highlighting the increased significance of intravenous drug accumulation over time[22].

Regarding the safety profile of sevoflurane among ICU patients, we did not observe significant changes among hemodynamics, laboratory organ failure markers, hypersensitivity/allergy or malignant hyperthermia. The prolonged exposure to sevoflurane has been restricted due to the risk of renal failure caused by fluoride accumulation[23]. However, a recent systematic review with meta-analysis noted that despite this elevation, sevoflurane was not linked to renal failure when utilized for critical care sedation lasting less than 72 hours[24]. On the other hand, in the surgical field, another meta-analysis did not find any association between the use of sevoflurane and postoperative renal impairment when compared with other agents used for anesthesia maintenance[25]. Longer-term studies in the ICU are needed to fully determine its true impact on the renal function of the critically ill patient population.

Historically, isoflurane and sevoflurane were administered in the ICU with the aid of vaporizers brought from the operating room, making their daily use impractical. Currently, with the increased availability of disposable vaporizers, their use could become more accessible. On the other hand, pharmacokinetics and pharmacodynamics knowledge, specialized equipment availability, including dedicated vaporisers and scavenging systems, could increase the logistical complexity of inhaled ICU sedation, and represents a paradigm shift for healthcare staff, moving away from the intravenous *status quo*[26]. In this sense, a recent survey conducted in France, targeting over 100 intensivists, 60% cited lack of familiarity and 58% cited lack of training for the teams as the primary reasons for not using inhaled sedation[27]. In our study we aimed to specifically explore and document the bedside barriers self-reported by attending physicians. The most significant referred issue was the obstruction of the anesthetic conserving device due to respiratory secretions. This problem is not unlike the obstruction of a bacterial viral filter or a heat-moisture exchanger, and it is typically resolved by replacing the anesthetic conserving device. However, if the patient's sedation relies solely on inhaled drugs, it could potentially lead to an unintended awakening. This study has several limitations that should be considered when interpreting the findings. Firstly, as it is a retrospective study with a small sample size and a limited number of participants, larger datasets are needed to draw definitive conclusions. Additionally, the measure used to record barriers to the use of inhaled sedatives relies on self-reporting by attending physicians. The accuracy of this information may vary among different physicians and clini-

cal scenarios, potentially introducing bias into our results. Furthermore, increasing the granularity of sedative dosage and vital signs recording, along with a longer-term follow-up, would enhance our understanding of the medium and long-term effects of these sedatives in the ICU population, providing avenues for future research. Despite these limitations, in our knowledge, this is the first study on inhaled sedatives in the region, conducted across two hospitals with a strong research background. This collaborative effort underscores the importance of exploring new tools for sedation in ICU settings.

In conclusion, we found that sevoflurane effectively achieved sedation goals and resulted in a reduction in opioid use. Our results align with previous trials assessing the effectiveness of inhaled sedatives, highlighting their safety and efficacy in ICU sedation. Overall, our study contributes to the growing body of evidence supporting the use of inhaled sedatives in ICU sedation, offering a potential alternative to intravenous sedation and remarking the need for continued research in this area.

Conflicts of interest: None to declare

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Supplementary material
Sedation with inhaled sevoflurane in the intensive care unit

STROBE guideline checklist

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6 5-6
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) If applicable, explain how loss to follow-up was addressed	
		(e) Describe any sensitivity analyses	
Results			
Participants	13	(a) Report numbers of individuals at each stage of study-eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	7-8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarize follow-up time (eg. average and total amount)	
Outcome data	15	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done-eg. analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarize key results with reference to study objectives	8-9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	10-11
		Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability			
Other information	21	Discuss the generalisability (external validity) of the study results	10-11
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

Table 1 | (Supplementary material). Data on invasive mechanical ventilation prior and during inhaled sedation

	Data on invasive mechanical ventilation																					
	Mode		FiO^2		TV		PEEPt		PlatP		RR		Flow		PeakP		DP		SC		MP	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
C1	VCV	VCV	45	50	360	370	14	14	23	22	26	28	43	30	27	31	9	8	40	46	23	26
C2	VCV	VCV	35	30	500	500	10	8	21	18	20	20	46	66	37	25	11	10	45	50	27	22
C3	VCV	VCV	40	40	550	540	10	10	19	19	14	24	68	46	22	29	9	9	61	60	17	30
C4	VCV	VCV	30	30	600	540	10	10	20	20	20	24	60	41	31	28	10	10	60	54	31	29
C5	VCV	VCV	21	50	550	550	6	10	15	20	14	16	-	55	23	30	9	10	61	55	-	22
C6	VCV	PCV	50	35	380	500	12	6	23	16	26	22	43	44	30	19	11	10	35	50	24	18
C7	VCV	VCV	50	50	480	480	8	8	22	20	18	20	45	45	25	23	14	12	34	40	17	18
C8	VCV	VCV	60	70	420	460	8	10	24	26	20	22	47	46	28	27	16	16	26	29	18	23
C9	PCV	PCV	45	50	480	420	8	12	19	21	20	22	-	50	24	27	11	9	44	47	-	22
C10	VCV	PCV	60	50	430	440	10	10	22	24	24	24	45	48	24	22	12	14	36	31	21	21
C11	VCV	VCV	80	30	420	395	8	8	22	20	16	16	47	40	21	18	14	12	30	33	12	10

C: case; pre: previous to inhaled sedation; post: during inhaled sedation; FiO_2: fraction of inspired oxygen; TV: tidal volume (ml); PEEPt: total positive end-expiratory pressure (cmH_2O); PlatP: plateau pressure (cmH_2O); RR: respiratory rate; Flow (liters/seg); PeakP: peak pressure (cmH_2O); DP: driving pressure (cmH_2O); SC: static compliance (ml/cmH_2O); MP: mechanical power (Joule/min); - : missing data