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Inhaled Sedation in Acute Respiratory Distress Syndrome
The SESAR Randomized Clinical Trial

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IMPORTANCE Whether the use of inhaled or intravenous sedation affects outcomes differentially in mechanically ventilated adults with acute respiratory distress syndrome (ARDS) is unknown.

OBJECTIVE To determine the efficacy and safety of inhaled sevoflurane compared with intravenous propofol for sedation in patients with ARDS.

DESIGN, SETTING, AND PARTICIPANTS Phase 3 randomized, open-label, assessor-blinded clinical trial conducted from May 2020 to October 2023 with 90-day follow-up. Adults with early moderate to severe ARDS (defined by a ratio of Pao_2 to the fraction of inspired oxygen of <150 mm Hg with a positive end-expiratory pressure of ≥8 cm H_2O) were enrolled in 37 French intensive care units.

INTERVENTIONS Patients were randomized to a strategy of inhaled sedation with sevoflurane (intervention group) or to a strategy of intravenous sedation with propofol (control group) for up to 7 days.

MAIN OUTCOMES AND MEASURES The primary end point was the number of ventilator-free days at 28 days; the key secondary end point was 90-day survival.

RESULTS Of 687 patients enrolled (mean [SD] age, 65 [12] years; 30% female), 346 were randomized to sevoflurane and 341 to propofol. The median total duration of sedation was 7 days (IQR, 4 to 7) in both groups. The number of ventilator-free days through day 28 was 0.0 days (IQR, 0.0 to 11.9) in the sevoflurane group and 0.0 days (IQR, 0.0 to 18.7) in the propofol group (median difference, −2.1 [95% CI, −3.6 to −0.7]; standardized hazard ratio, 0.76 [95% CI, 0.50 to 0.97]). The 90-day survival rates were 47.1% and 55.7% in the sevoflurane and propofol groups, respectively (hazard ratio, 1.31 [95% CI, 1.05 to 1.62]). Among 4 secondary outcomes, sevoflurane was associated with higher 7-day mortality (19.4% vs 13.5%, respectively; relative risk, 1.44 [95% CI, 1.02 to 2.03]) and fewer intensive care unit–free days through day 28 (median, 0.0 [IQR, 0.0 to 6.0] vs 0.0 [IQR, 0.0 to 15.0]; median difference, −2.5 [95% CI, −3.7 to −1.4]) compared with propofol.

CONCLUSIONS AND RELEVANCE Among patients with moderate to severe ARDS, inhaled sedation with sevoflurane resulted in fewer ventilator-free days at day 28 and lower 90-day survival than sedation with propofol.

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Visual Abstract
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Supplemental content

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Acute respiratory distress syndrome (ARDS) is frequent in patients admitted to an intensive care unit (ICU) and is associated with high hospital mortality rates (35%-46%).[1] Mechanical ventilation remains crucial in managing patients with ARDS,[2] often requiring sedation to improve tolerance and synchrony.[3] However, optimal sedation choice remains unclear.

Guidelines recommend light sedation with nonbenzodiazepine sedatives, such as propofol or dexmedetomidine, in critically ill, ventilated patients (conditional recommendation with a low quality of evidence).[4] However, specific guidance for sedation in patients with ARDS is lacking owing to sparse evidence. Deep sedation and neuromuscular blockade may be required to facilitate lung-protective ventilation during moderate to severe ARDS.[5] Propofol, despite potential adverse effects during high-dose or prolonged use, is often favored for its titratability and organ-independent clearance.[5,6]

Inhaled volatile anesthetics are emerging alternatives, although evidence in patients with ARDS remains scarce. In a pilot trial involving patients with moderate to severe ARDS, inhaled sevoflurane was feasible, improved oxygenation, and decreased markers of inflammation and lung epithelial injury compared with midazolam.[7] A noninferiority trial comparing inhaled isoflurane with propofol in invasively ventilated ICU patients supported the efficacy and safety of inhaled sedation,[8] and a systematic review found that inhaled sedation was associated with faster awakening and extubation than intravenous sedation.[9] However, these findings may not apply to patients with ARDS.

The current study hypothesized that inhaled sedation with sevoflurane could increase the number of days alive and free of mechanical ventilation in patients with ARDS. Thus, the Sevoflurane for Sedation in ARDS (SESAR) trial was conducted to determine the efficacy and safety of early sedation with inhaled sevoflurane compared with propofol in patients with moderate to severe ARDS.

Key Points

Question Is a strategy of inhaled sedation with sevoflurane safe and associated with improved clinical outcomes in patients with acute respiratory distress syndrome compared with a strategy of intravenous sedation with propofol?

Findings In this randomized clinical trial that included 687 intensive care unit patients with moderate to severe acute respiratory distress syndrome, inhaled sedation with sevoflurane resulted in fewer ventilator-free days at 28 days and lower survival at 90 days than intravenous sedation with propofol.

Meaning These findings do not support a strategy of inhaled sedation with sevoflurane in critically ill patients with moderate to severe acute respiratory distress syndrome.

Methods

Trial Design and Oversight

We conducted this investigator-initiated, multicenter, open-label, assessor-blinded, randomized trial in 37 ICUs in France. The trial was sponsored by the University Hospital of Clermont-Ferrand (France) and funded by the French Ministry of Health, the European Society of Anesthesiology and Intensive Care, and Sedana Medical.

The trial protocol,[10] which was approved by an ethics committee (Comité de Protection des Personnes Ile-de-France 2) and the French medicines agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé), and initial and modified statistical analysis plans are available in Supplement 1. The trial was registered with ClinicalTrials.gov (NCT04235608) and its report follows the Consolidated Standards of Reporting Trials reporting guidelines and checklist.

Patients or their legally authorized representative provided written informed consent. Additional details on methods are available in the eMethods in Supplement 2.

Patient Selection and Randomization

We enrolled adult patients (≥18 years of age) who were undergoing invasive mechanical ventilation and met the Berlin definition criteria for less than 24 hours,[11] with a ratio of Pao_2 to the fraction of inspired oxygen (FIO_2) of less than 150 mm Hg and a positive end-expiratory pressure (PEEP) of 8 cm H_2O or more. Patients were excluded if they were pregnant; had suspected or proven intracranial hypertension; had long QT syndrome; had history of (or predisposition for) malignant hyperthermia or liver disease from volatile anesthetics; had hypersensitivity to sevoflurane, propofol, or cisatracurium; had persistent bronchopleural fistula; or had received mechanical ventilation for more than 120 hours before enrollment. Further details are provided in the eMethods in Supplement 2.

Patients were randomly assigned by local investigators using a web-based system in a 1:1 ratio to receive sevoflurane or propofol. Randomization was stratified by site, ARDS severity (Pao_2:FIO_2 <100 mm Hg or ≥100 mm Hg), suspected or proven COVID-19, and shock (defined as the intravenous infusion of vasoactive drugs).

Trial Interventions and Measurements

All patients initially received deep sedation, targeting a score on the Richmond Agitation-Sedation Scale (RASS) of −5 to −4 (range: −5 [unresponsive] to 4 [combative], with 0 meaning alert and calm),[12] with subsequent neuromuscular blockade using continuous cisatracurium infusion for up to 48 hours, or until Pao_2:FIO_2 of at least 150 mm Hg for 4 hours or more with an FIO_2 of 0.6 or lower. Then, the use of light sedation (RASS score, −1 to 0) was recommended with daily awakening and spontaneous-breathing trials. Initial deep sedation with cisatracurium was believed to be a common and clinically relevant approach to patients with severe hypoxemia, as per available guidelines when designing the trial.[13] In both groups, patients received the allocated intervention until the trial drug was permanently discontinued or until the 7-day intervention period, whichever came first. Patients resumed the trial drug if sedation was indicated within the 7-day intervention period. We treated pain on an analgesia-first approach to sedation, with opioid use as necessary.[5] After day 7, clinicians decided on sedation and other interventions. Patients received low-tidal-volume ventilation and a high PEEP strategy.[14]

The protocol involved waiting 12 hours after ARDS onset before prone positioning.[14,15]

In the intervention group, sevoflurane was administered via a miniaturized anesthetic conserving device (Sedaconda ACD-S, Sedana Medical) placed between the endotracheal tube and ventilator circuit, with expired gas scavenged per manufacturer instructions. The control group received intravenous propofol.

Trial End Points

The primary end point was the number of days alive and off invasive mechanical ventilation (ventilator-free days) from randomization through day 28, as it accounts for both death and the time to extubation. If a patient died prior to day 28, the number of ventilator-free days was zero. The key secondary efficacy end point was 90-day survival. Other secondary efficacy end points were mortality at 7, 14, and 28 days and hospital mortality at 28 days after randomization. Safety end points included changes in hemodynamic measures and in the Kidney Disease: Improving Global Outcomes[16] criteria for acute kidney injury through day 7[17]; new-onset supraventricular tachycardia or atrial fibrillation; severe hypercapnic acidosis with arterial pH less than 7.15; and development of malignant hyperthermia, propofol-related infusion syndrome, pneumothorax, or bronchopleural fistula persistent despite drainage through day 7. Additional details regarding exploratory end points, along with a list of additional end points not reported here, are provided in the eMethods in Supplement 2.

Statistical Analysis

Under the hypothesis of a 28-day mortality rate of 30% to 35%[18,19] and the assumption that the variability of the number of ventilator-free days at 28 days would follow the properties of the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial,[18] we calculated that enrolling 680 patients would provide the trial with more than 80% power to detect a mean difference of 2 ventilator-free days at 28 days with a standard deviation of 8. We therefore included 350 in each group. After the blinded interim analysis of 350 patients, the independent data and safety monitoring committee recommended continuing the trial.

The primary analysis was an unadjusted, modified intention-to-treat comparison of the primary end point in the 2 groups, with the use of a mixture of generalized gamma distributions with death as the competing event.[20] Results are presented as median differences and standardized hazard ratios with 95% confidence intervals (CIs). The event of interest was successful weaning from invasive mechanical ventilation and the competing event was death. If π is the proportion of the total population of patients who achieve successful weaning from invasive mechanical ventilation and $(1 - \pi)$ is the complementary proportion of patients who die within 28 days, a mixture according to π and $(1 - \pi)$ of 2 generalized gamma distributions were used to model times to successful weaning from invasive mechanical ventilation and times to death, considering maximum likelihood for parameter estimation and the likelihood ratio tests to compare nested models.

We also analyzed 2 per-protocol populations and performed 2 adjusted analyses. Day-90 survival was evaluated using the Kaplan-Meier approach and compared using the log-rank test and marginal Cox proportional hazard regression. Adjusted analyses were conducted, and results were expressed as hazard ratios with 95% CIs. Categorical variables were analyzed using the χ^2 or Fisher exact test. Continuous parameters were compared using a *t* test or Mann-Whitney *U* test. Longitudinal data were analyzed with a random-effects model. Subgroup analyses were performed to assess the consistency of the treatment effect across prespecified subgroups, including interaction terms. The widths of CIs were not adjusted for multiplicity and should be interpreted as exploratory. A 2-sided *P* value of less than .05 was considered to indicate statistical significance. All analyses were performed using Stata version 15.0 (StataCorp).

Results

Patients

From May 2020 through October 2023, we screened 2016 patients, of whom 1316 (65%) met at least 1 exclusion criterion or were not included for other reasons (**Figure 1**). Of the 700 patients who were enrolled and randomized, 13 were excluded (4 in the sevoflurane group and 9 in the propofol group) and 687 patients were included in the primary analysis (346 in the sevoflurane group and 341 in the propofol group). The trial groups had similar characteristics before randomization (**Table 1**; eTable 1 in Supplement 2). Patients were enrolled a median of 1 day (IQR, 0-3) after ICU admission; 54.9% had a diagnosis of COVID-19 pneumonia, with a median Pao_2:FIo_2 at enrollment of 111 mm Hg (IQR, 86-137) and 107 mm Hg (IQR, 80-133) in the sevoflurane and propofol groups, respectively. Additional details are available in the eResults in Supplement 2.

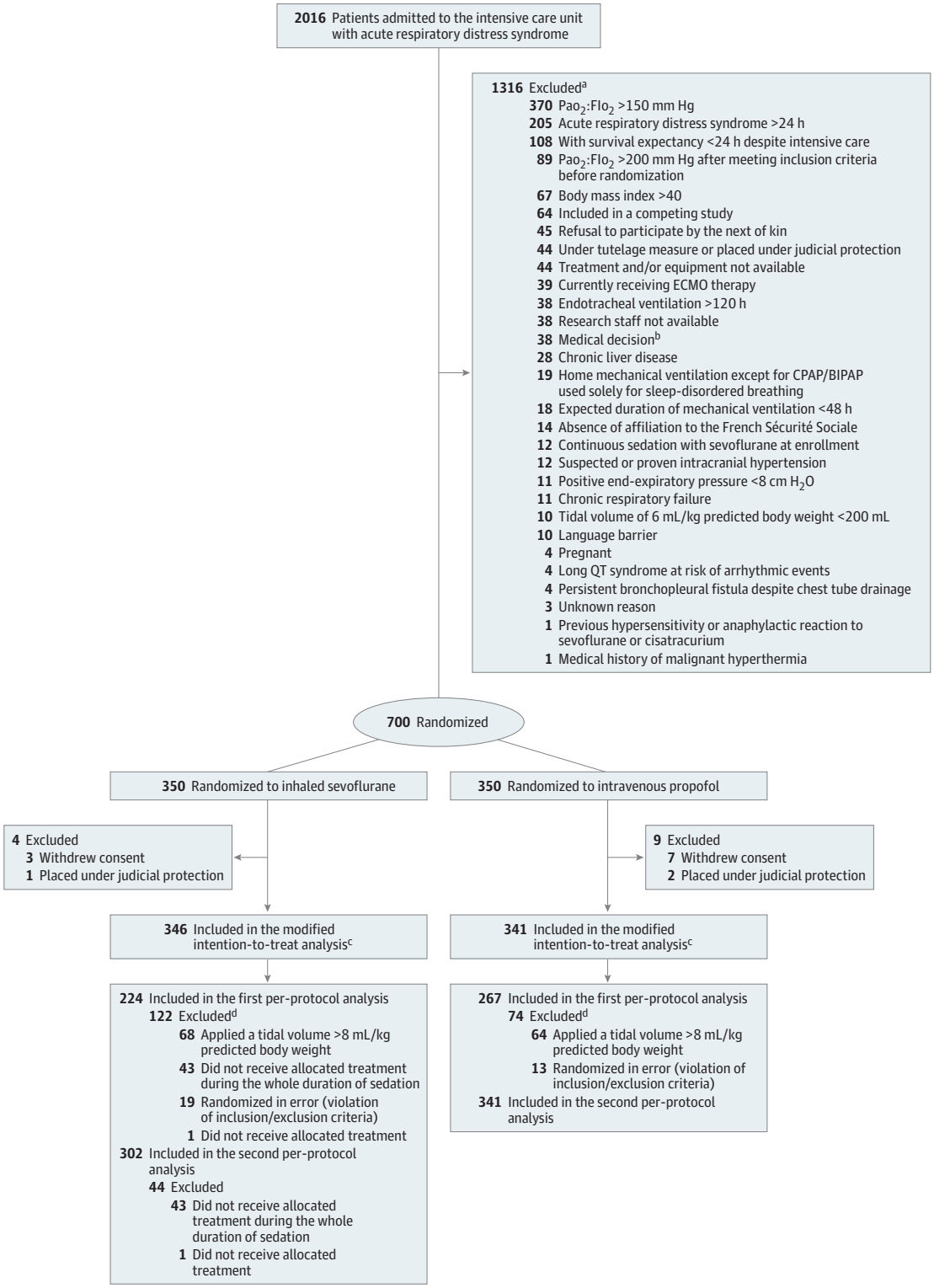
Trial Interventions and Other Care Processes

The percentage of patients receiving sedation before randomization was similar in the 2 groups (Table 1). Details on trial drugs and sedation regimens are shown in eTable 2 in Supplement 2.

Of the 687 patients who underwent randomization, 1 patient allocated to the sevoflurane group and 1 patient allocated to the propofol group did not receive the assigned trial drug. During the 7-day intervention period, median durations of trial drug administration were 5 days (IQR, 2-7) in the sevoflurane group and 6 days (IQR, 3-7) in the propofol group. The total median sedation duration was 7 days (IQR, 4-7) in both groups.

During the first 48 hours after randomization, deep sedation (RASS score of −5 to −4) was achieved in 93.9% of patients in the sevoflurane group and 89.2% of patients in the propofol group (eFigure 1 and eTable 2 in Supplement 2). During the 7-day intervention period, additional sedation was used in 148 patients in the sevoflurane group and in 64 patients in the propofol group (eFigure 2 and eTable 2 in Supplement 2). During the first 48 hours, 72.1% of patients in the sevoflurane group and 70.0% of patients in the propofol group received neuromuscular blockade infusion, with a total median neuromuscular blockade duration of 5 days (IQR, 2-9) in both groups (eTable 2 in Supplement 2).

Figure 1. Patient Screening, Enrollment, and Follow-Up in the Sevoflurane for Sedation in ARDS (SESAR) Trial



CPAP/BIPAP indicates continuous positive airway pressure/bilevel positive airway pressure; ECMO, extracorporeal membraine oxygenation; and FIo_2, fraction of inspired oxygen.

[a]Each patient could have more than 1 reason for exclusion.

[b]Reasons included unknown reason (n = 22), clinical deterioration (n = 8), ventilation or sedation deemed difficult (n = 3), pneumothorax (n = 2), low fraction of inspired oxygen (n = 2), and lung ventilation (n = 1).

[c]Included all patients who underwent randomization except those who withdrew consent or were under judicial protection.

[d]Each patient could have more than 1 protocol violation.

Table 1. Characteristics of the Patients Before Randomization[a]

Characteristic	No. (%)	
	Inhaled sevoflurane (n = 346)	Intravenous propofol (n = 341)
Age, mean (SD), y	64.9 (12.6)	64.4 (12.3)
Sex		
Female	111 (32.1)	92 (27.0)
Male	235 (67.9)	249 (73.0)
BMI, mean (SD)	28.9 (5.4)	28.6 (5.4)
No.	345	337
Time from ICU admission to randomization, median (IQR), d	1 (0-3)	1 (0-3)
Randomization on the same day as ICU admission	108 (31.2)	16 (34.0)
Time from intubation to randomization, median (IQR), d	0 (0-1)	0 (0-1)
Randomization on the same day as intubation	209 (60.4)	221 (64.8)
Primary cause of lung injury		
Pneumonia	288 (83.2)	289 (84.8)
Suspected or confirmed COVID-19 pneumonia	189 (54.6)	188 (55.1)
Aspiration	32 (9.3)	30 (8.8)
Extrapulmonary sepsis	30 (8.7)	25 (7.3)
Other cause[b]	19 (5.5)	26 (7.6)
Pancreatitis	10 (2.9)	9 (2.6)
Drug intoxication	7 (2.0)	2 (0.6)
Severe trauma	4 (1.2)	4 (1.2)
Need for vasopressor or inotropic support before randomization	254 (73.4)	256 (75.1)
Norepinephrine, No./total (%)	253/254 (99.6)	251/256 (98.0)
Dobutamine, No./total (%)	5/254 (2.0)	11/256 (4.3)
Serum lactate, median (IQR), mmol/L[c]	1.6 (1.2-2.3)	1.6 (1.2-2.2)
No.	318	313
KDIGO criteria for acute kidney injury before randomization[d]		
No acute kidney injury	219 (63.3)	224 (65.7)
Stage 1	37 (10.7)	41 (12.0)
Stage 2	47 (13.6)	38 (11.1)
Stage 3	43 (12.4)	38 (11.1)
Need for kidney replacement therapy	10 (2.9)	9 (2.6)
Antibiotic therapy	274 (79.2)	275 (80.7)
Corticosteroid therapy	233 (67.3)	223 (65.4)
Sedation received before randomization, No./total (%)	336/346 (97.1)	332/341 (97.4)
Propofol	289/336 (86.0)	301/332 (90.7)
Dexmedetomidine	5/336 (1.5)	2/332 (0.6)
Benzodiazepine	69/336 (20.5)	51/332 (15.4)
Other (clonidine, ketamine, or levomepromazine)	4/336 (1.2)	2/332 (0.6)
Respiratory support before intubation		
High-flow oxygen therapy	222 (64.2)	230 (67.4)
Noninvasive ventilation	161 (46.5)	161 (47.2)
Ventilator mode before randomization		
Volume controlled	329 (95.1)	320 (93.8)
Pressure controlled	14 (4.0)	17 (5.0)
Pressure support ventilation	1 (0.3)	3 (0.9)
Airway pressure release ventilation	1 (0.3)	0
Other mode	1 (0.3)	1 (0.3)
Respiratory parameters before randomization		
Pao_2:FIo_2, median (IQR), mm Hg	111 (86-137)	107 (80-133)
No.	344	340
Tidal volume, median (IQR), mL/kg of predicted body weight	6.1 (5.7-6.7)	6.0 (5.6-6.6)
No.	339	333
Respiratory rate, median (IQR), breaths/min	26 (22-28)	26 (24-28)
No.	342	334
Positive end-expiratory pressure, median (IQR), cm H_2O	10 (8-12)	10 (8-13)
No.	343	337
Prone position before randomization, No./total (%)	99/263 (37.6)	97/265 (36.6)
Continuous neuromuscular blockade, No./total (%)	240/264 (90.9)	228/266 (85.7)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FIo_2, fraction of inspired oxygen; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes.

SI conversion factors: To convert creatinine to mg/dL, divide by 88.4; and lactate to mg/dL, divide by 0.111.

[a] There were no significant between-group differences before randomization. Percentages may not total 100 because of rounding.

[b] Other causes are reported in eTable 1 in Supplement 2.

[c] Normal serum lactate levels range from 0.5 to 2.0 mmol/L.

[d] Acute kidney injury was defined using the KDIGO criteria for acute kidney injury (increase in serum creatinine level by ≥26.5 µmol/L [≥0.3 mg/dL] within 48 hours; or increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 mL/kg/h for 6 hours). Higher stages of KDIGO criteria for acute kidney injury reflect higher severity.[16] Stage 1 was defined as an increase in serum creatinine level by ≥26.5 µmol/L (≥0.3 mg/dL) or to 1.5 to 1.9 times the baseline value, and/or urine volume <0.5 mL/kg/h for 6 to 12 hours. Stage 2 was defined as an increase in serum creatinine level to 2.0 to 2.9 times the baseline value, and/or urine volume <0.5 mL/kg/h for ≥12 hours. Stage 3 was defined as an increase in serum creatinine level by ≥353.6 µmol/L (≥4.0 mg/dL) or to at least 3.0 times the baseline value or initiation of kidney replacement therapy, and/or urine volume <0.3 mL/kg/h for ≥24 hours or anuria for ≥12 hours.

Tidal volumes and PEEP levels during the 7-day intervention period were in accordance with the trial protocol in both groups (**Table 2**; eTable 3 in Supplement 2). Details regarding respiratory, hemodynamic, kidney, laboratory data, and other treatments received during the 7-day intervention period are provided in eTables 3 through 7 in Supplement 2.

Primary End Point

At day 28, the median number of ventilator-free days was 0.0 (IQR, 0.0 to 11.9) in the sevoflurane group and 0.0 (IQR,

Table 2. Primary and Secondary End Points[a]

Variable	Inhaled sevoflurane (n = 346)	Intravenous propofol (n = 341)	Between-group difference (95% CI)[b]	Treatment effect (95% CI)[c]
Primary end point				
Ventilator-free days through day 28, median (IQR)	0.0 (0.0 to 11.9)	0.0 (0.0 to 18.7)	−2.1 (−3.6 to −0.7)	0.76 (0.50 to 0.97)
Key secondary end point				
Death at day 90, No./total (%)	183/346 (52.9)	151/341 (44.3)	8.6 (1.2 to 16.1)	1.31 (1.05 to 1.62)
Secondary end points				
Mortality, No./total (%)[d]				
At 28 d	152/345 (44.1)	132/340 (38.8)	5.2 (-2.1 to 12.6)	1.13 (0.95 to 1.36)
At 14 d	104/345 (30.1)	90/340 (26.5)	3.7 (-3.1 to 10.4)	1.14 (0.90 to 1.45)
At 7 d	67/345 (19.4)	46/340 (13.5)	5.9 (0.4 to 11.4)	1.44 (1.02 to 2.03)
ICU-free days through day 28, median (IQR)	0.0 (0.0 to 6.0)	0.0 (0.0 to 15.0)	−2.5 (−3.7 to −1.4)	0.67 (0.52 to 0.86)
No.	345	341		
Safety secondary end points through day 7				
Mean arterial pressure, median (IQR), mm Hg	80 (75 to 86)	81 (76 to 87)	-1.12 (-2.38 to 0.14)	NR
No. of patients/total patient-days[e]	346/2423	346/2501		
Dose of infused norepinephrine, median (IQR), µg/kg/min	0.31 (0.17 to 0.63)	0.23 (0.12 to 0.49)	0.07 (0.03 to 0.10)	NR
No. of patients/total patient-days[e]	330/1480	308/1398		
Dose of infused epinephrine, median (IQR), µg/kg/min	2.2 (2.2 to 2.2)	0.9 (0.1 to 3.0)	Not estimated[f]	NR
No. of patients/total patient-days[e]	1/1	3/4		
Dose of infused dobutamine, median (IQR), µg/kg/min	3.1 (2.5 to 5.0)	4.2 (2.5 to 5.4)	-1.04 (-2.71 to 0.62)	NR
No. of patients/total patient-days[e]	19/56	28/88		
Serum lactate, median (IQR), mmol/L	1.7 (1.4 to 2.2)	1.6 (1.3 to 2.0)	0.12 (0.02 to 0.23)	NR
No. of patients/total patient-days[e]	344/2137	341/2173		
KDIGO criteria for acute kidney injury, No. (%)[g]				
No acute kidney injury	110 (31.8)	146 (42.8)	-0.11 (-0.18 to -0.04)	1 [Reference]
Stage 1	59 (17.1)	41 (12.0)	0.05 (-0.01 to 0.10)	1.91 (1.62 to 2.25)
Stage 2	61 (17.6)	62 (18.2)	-0.01 (-0.06 to 0.05)	1.31 (1.12 to 1.52)
Stage 3	116 (33.5)	92 (27.0)	0.07 (-0.01 to 0.14)	1.67 (1.47 to 1.91)
Predefined adverse events, No. (%)				
Supraventricular tachycardia or atrial fibrillation	27 (7.8)	23 (6.7)	−0.01 (−0.05 to 0.11)	1.16 (0.68 to 1.98)
Severe hypercapnic acidosis with pH <7.15	11 (3.2)	5 (1.5)	1.7 (−0.5 to 4.0)	2.17 (0.76 to 6.18)
Malignant hyperthermia	2 (0.6)	0	0.6 (−0.2 to 1.4)	Not estimated[f]
Propofol-related infusion syndrome	0	3 (0.9)	−0.9 (−1.9 to 0.1)	Not estimated[f]
Pneumothorax or bronchopleural fistula persistent despite drainage	1 (0.3)	0	0.3 (−0.3 to 0.9)	Not estimated[f]

Abbreviations: ICU, intensive care unit; NR, not relevant; KDIGO, Kidney Disease: Improving Global Outcomes.

[a] The primary end point was the number of ventilator-free days as calculated from randomization to day 28. All the patients who had died by day 28 were considered to have had no ventilator-free days. Percentages may not total 100 because of rounding.

[b] The between-group difference is reported as the median difference (95% CI) for ventilator-free days, ICU-free days, and continuous variables such as arterial pressure, vasopressor dose, or serum lactate or the absolute difference (95% CI) for categorical variables (such as mortality or stages of acute kidney injury).

[c] The treatment effect is reported as the standardized hazard ratio (95% CI) for ventilator-free days and ICU-free days, the hazard ratio (95% CI) for 90-day survival, or the relative risk (95% CI) for categorical variables (such as mortality or stages of acute kidney injury).

[d] Hospital mortality and all-cause mortality were identical at 28 days as all deaths occurred in the hospital in both groups.

[e] Numbers are reported as the number of patients with the variable available (No.) and the total number of patient-days during which the variable is available from randomization through day 7. Daily values can be found in eTable 20 in Supplement 2.

[f] The between-group difference or relative risk was not estimated due to a limited number of occurrences.

[g] Acute kidney injury was defined using the KDIGO criteria for acute kidney injury. Highest stages of KDIGO criteria for acute kidney injury were recorded through day 7. Higher stages reflect higher severity.[16]

0.0 to 18.7) in the propofol group (median difference, −2.1 [95% CI, −3.6 to −0.7]; standardized hazard ratio, 0.76 [95% CI, 0.50 to 0.97]) (Table 2; eFigure 3 in Supplement 2). There was no evidence of heterogeneity in predefined subgroups (eTable 8 in Supplement 2). Results were similar in the 2 per-protocol populations, after multivariable adjustments, and in a sensitivity analysis excluding the first 5 patients enrolled at each trial site (eTables 9 through 12 in Supplement 2).

Secondary End Points

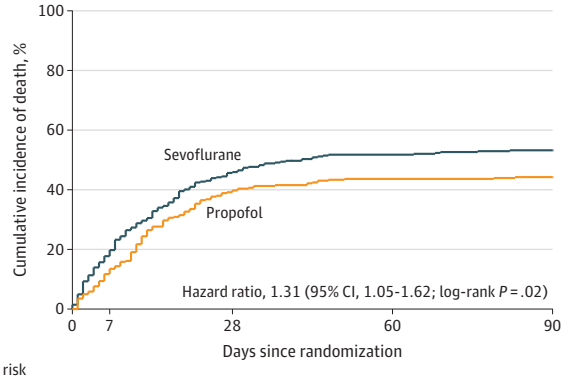
Survival by day 90 (the key secondary end point) was lower in the sevoflurane group (163 survivors/346 patients, 47.1%) than in the propofol group (190 survivors/341 patients, 55.7%) (hazard ratio, 1.31 [95% CI, 1.05-1.62]; P = .02 using the log-rank test) (Table 2 and **Figure 2**). Results were unchanged after adjustment (eTable 13 in Supplement 2). The cumulative number of patients who died, were extubated, or were discharged from the ICU is reported in **Figure 3**. The main causes of death are reported in eTable 14 in Supplement 2.

Per-protocol analyses showed similar results for all secondary end points. Among all prespecified subgroup analyses, the only significant difference was heterogeneity between treatment groups and suspected or proven COVID-19 before randomization (as defined a priori as a subgroup analysis), with respect to 90-day survival (P = .01 for treatment by subgroup interaction) and 28-day mortality (P = .003 for treatment by subgroup interaction) (eFigures 4 and 5 and eTables 15 through 19 in Supplement 2).

Safety End Points and Adverse Events

Safety end points are summarized in Table 2 and eTable 20 in Supplement 2. Median norepinephrine doses from randomization to day 3 and changes in median serum lactate levels from randomization to days 1, 2, and 4 were higher in the sevoflurane group than in the propofol group. Similarly, fewer patients in the sevoflurane group than in the propofol group were free from acute kidney injury through day 7 (between-group difference, -0.11 [95% CI, -0.18 to -0.04]) (Table 2; eTable 5 and eFigure 6 in Supplement 2). There were no between-group differences in predefined adverse events (Table 2). Nephrogenic diabetes insipidus was reported in 5 patients (1.4%) in the sevoflurane group (median time since randomization, 5.8 days [IQR, 4.3-5.9]) and did not occur in the propofol group (absolute difference, 1.4 [95% CI, 0.2-2.7]). Exploratory end points are reported in eTable 21 in Supplement 2.

Figure 2. Kaplan-Meier Estimates of 90-Day Survival in the Modified Intention-to-Treat Population



No. at risk

Sevoflurane	346	283	192	164	159
Propofol	341	301	210	189	186

At 90 days, 183 of 346 patients (52.9%) in the sevoflurane group and 151 of 341 patients (44.3%) in the propofol group had died. The median follow-up times were 40.5 days (IQR, 10.0-90.0) in the sevoflurane group and 90.0 days (IQR, 14.0-90.0) in the propofol group.

Discussion

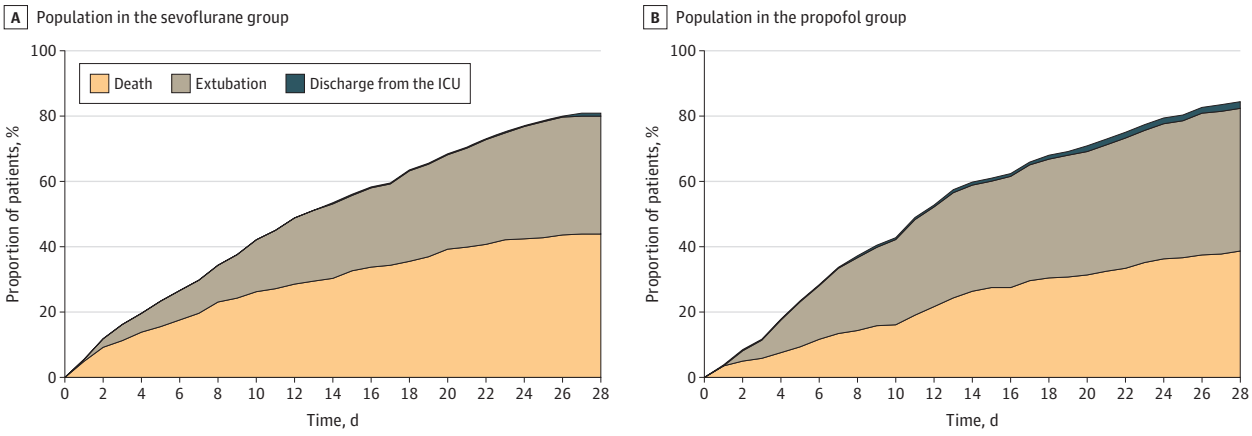
Among adults with moderate to severe ARDS enrolled in this multicenter, randomized trial, inhaled sedation with sevoflurane resulted in fewer ventilator-free days at 28 days than intravenous sedation with propofol. Moreover, survival at 90 days was lower among those patients who received inhaled sevoflurane.

The potential benefit of inhaled sedation in ARDS was based on evidence suggesting anti-inflammatory and lung-protective effects of volatile anesthetics.[7,21] Small trials and observational studies in critically ill patients suggested shorter wake-up times and duration on mechanical ventilation with volatile anesthetics compared with intravenous hypnotics.[9] These data supported a potential clinical benefit of sevoflurane in ARDS and the choice of ventilator-free days as the primary end point.

The findings of the current study contrast with evidence suggesting benefits of volatile anesthetics, such as sevoflurane or isoflurane, in patients without ARDS.[9] They also challenge proposed oxygenation benefits in ARDS, suggested by smaller and preclinical studies.[7,22-24] This lack of effect was confirmed in subsequent clinical studies in patients with hypoxemic acute respiratory failure.[25,26] While a single-center trial showed improved oxygenation with sevoflurane vs midazolam in moderate to severe ARDS (but no mortality difference),[7] inhaled anesthetic use, popularized during COVID-19 sedative shortages[27] and associated with reduced sedative and analgesic needs,[28] yielded mixed results regarding oxygenation and mortality in patients with COVID-19.[29-31] Although between-group differences in 90-day survival and 28-day mortality were greater in patients without COVID-19, possibly reflecting worse prognosis in controls with COVID-19, no significant treatment-by-subgroup interactions were found for the primary and other secondary end points, suggesting relevance of current findings regardless of ARDS etiology.

A particular feature of the SESAR trial was the use of early deep sedation with neuromuscular blockade, before transitioning to lighter sedation as oxygenation improved.[32] A stabilization period before prone positioning of at least 12 hours after the onset of ARDS was recommended, as suggested by current evidence.[18,32] Despite standardized training, variability in expertise with inhaled sedation could have influenced results. The enrolled population is unlikely to explain the findings, as both groups had similar ARDS severity and vasopressor needs, with control group mortality aligning with the ROSE

Figure 3. Cumulative Numbers of Patients Dead, Extubated (Alive), and Discharged (Alive) From the Intensive Care Unit From Randomization Through Day 28 in the Modified Intention-to-Treat Population



Extubation (alive) was counted as the end of the last period of assisted breathing to day 28. ICU indicates intensive care unit.

trial.[18] The prolonged sedation and cisatracurium use in SESAR may raise concerns about generalizability, but the alignment of clinical outcomes in the control group with those in recent trials[18,19] suggests the current findings remain applicable to contemporary ARDS management, despite variations in sedation practices.

Several hypotheses may explain the worse clinical outcomes in the sevoflurane group. Sevoflurane was associated with modest yet significant increases in serum lactate and norepinephrine dose within the first week after randomization. Whether this reflects more severe shock or vasoplegia due to sevoflurane or could account for the clinical outcomes observed with sevoflurane remains unclear. Prolonged sevoflurane use was associated with increased acute kidney injury, contrasting with the results from a systematic review[33] but aligning with those from a recent COVID-19 trial in which 39% of patients developed acute kidney injury.[25] Differences in prerandomization characteristics are unlikely to explain such differences. Consistent with previous studies after prolonged sevoflurane use,[21] the current study observed an increased incidence of nephrogenic diabetes insipidus, the precise mechanisms of which remain unknown.[34] Although their association with nephrotoxicity remains discussed,[21] high fluoride levels may have developed under sevoflurane, which was not verified in this study. This study's findings also differ from those of a recent systematic review of inhaled sedation in ICU patients, which included 9 smaller trials evaluating the same vaporizer device as in this trial.[9] Elevated arterial carbon dioxide and lower pH suggest issues with dead space (50 mL according to the manufacturer) or carbon dioxide retention from the device, potentially leading to the observed increases in ventilatory ratio, a predictor of ARDS mortality.[35] While the device used in the trial has low dead space and carbon dioxide retention risk,[21,36] it may have contributed to these issues. Although dead space volumes of heat and moisture exchangers or use of active humidifiers in the propofol group were not collected, whether the intervention increased mechanical power due to higher respiratory rates and influenced the risk of ventilator-induced lung injury deserves further investigation (eTables 3 and 21 in Supplement 2).[37] The Sedating With Volatile Anesthetics Critically Ill COVID-19 Patients in ICU (SAVE-ICU) trial (NCT04415060) will provide more safety data.

Our findings may have important clinical implications because inhaled sedation has garnered growing attention in ICU patients with ARDS or those at risk for the syndrome.[29] However, this trial does not inform whether outcomes would have differed with shorter durations of sevoflurane or with the use of other volatile anesthetics such as isoflurane. Such knowledge gaps may be addressed by ongoing trials of inhaled isoflurane sedation for mechanically ventilated ICU patients (NCT05312385 and NCT05327296).

Limitations

The trial has limitations. First, double-blinding was impossible due to the intervention's nature, though similar sedation scores in both groups suggest minimal performance bias. Second, data on volumes of fluid administered, sevoflurane's expired fractions, corticosteroid dosing, or concomitant opioid analgesia were not collected. Third, adherence with the ABCDEF (awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility) bundle was not assessed,[4] anticipating consistent care between groups. Fourth, COVID-19 pneumonia was the predominant ARDS cause; generalizability across ARDS causes or subphenotypes remains unknown. Fifth, the trial was unable to assess sevoflurane's impact on delirium,[38] and long-term and biological outcomes will be explored in future analyses.

Conclusions

In this trial involving patients with moderate to severe ARDS, inhaled sedation with sevoflurane resulted in fewer ventilator-free days and lower 90-day survival than did intravenous propofol.

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Group Information: The SESAR Trial Investigators appear in Supplement 3.

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Data Sharing Statement: See Supplement 4.

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