EDITORIAL

Sevoflurane Sedation in Acute Respiratory Distress Syndrome
Time to Put It to Sleep

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Acute respiratory distress syndrome (ARDS) is characterized by hypoxemic respiratory failure and inflammatory injury to the lungs, and occurs in 10% of all intensive care unit admissions. ARDS accounts for nearly a quarter of all patients requiring invasive mechanical ventilation and is associated with hospital mortality approaching 30% to 40%.[1] There are multiple large randomized trials on how to ventilate the patient with ARDS, when to prone the patient, and whether there is a role for adjunct therapy such as corticosteroids or neuromuscular blockade. There are few published data, however, on the optimal sedation strategy for patients with ARDS.[2]

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Patients with ARDS receiving invasive mechanical ventilation often require sedation and analgesia for prolonged periods for the relief of pain, discomfort, and anxiety. Both the choice of agents and the intensity of sedation in ARDS are a matter of debate. Typically, patients are sedated with systemic agents given intravenously, such as propofol, benzodiazepines such as midazolam, and dexmedetomidine. Adverse effects are common: all can cause hypotension; prolonged propofol use can cause hypertriglyceridemia, propofol infusion syndrome, and activation of the inflammatory response; other intravenous agents also have unanticipated immunomodulatory effects[3,4]; and opioid and benzodiazepine use can cause dependence and delirium.[5]

Inhalational anesthetic agents, such as isoflurane and sevoflurane, are ubiquitous in the operating room and typically last for a few hours, but until recently have rarely been used in the intensive care unit, where prolonged periods of sedation are often required. However, such agents could be beneficial for critically ill patients with respiratory failure both because of their sedative properties and because of their potentially salutary anti-inflammatory, bronchodilatory, and pulmonary vasodilatory effects.[6-8] A randomized clinical trial of isoflurane compared with propofol in critically ill patients receiving mechanical ventilation reported shorter time to extubation.[9] A pilot randomized clinical trial evaluating sevoflurane for 48 hours compared with midazolam in patients with ARDS reported that sevoflurane improved oxygenation and reduced inflammatory injury to the lungs.[10]

In this issue of *JAMA*, Jabaudon and colleagues[11] report the results of a multicenter trial comparing the effect of sedation strategies with inhaled sevoflurane vs propofol on clinical outcomes in patients with moderate to severe ARDS (defined by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of <150 mm Hg with a positive end-expiratory pressure of ≥8 cm H_2O). The investigators enrolled 687 participants, across 37 French intensive care units, who were randomized to either sedation with sevoflurane (intervention, n = 346) or propofol (control, n = 341) for up to 7 days. The primary outcome was the number of days alive and free of invasive ventilation (where patients dying were assigned zero days); secondary outcomes included 90-day mortality. The interventions were necessarily unblinded to the clinical team, but outcome assessors were blinded. The protocol allowed the use of propofol as cosedation in the intervention group; sedation in both groups was titrated to a clinical sedation score. All patients received low tidal volume ventilation with high positive end-expiratory pressure within 2 hours of randomization, continuing for up to 7 days. The choices of sedation after day 7, respiratory rescue therapies, and weaning from mechanical ventilation were left to the clinicians.

Patients assigned to receive sevoflurane had fewer ventilator-free days (median difference of 2 days), and numerically higher mortality at 90 days (53.2% vs 44.3%) compared with those in the propofol group. The difference in mortality appeared evident by day 7 (19.4% vs 13.5%). Of note, the difference in mortality rates at day 90 between sevoflurane and the propofol groups was most pronounced in the non-COVID-19 ARDS subgroup (51.6% for sevoflurane vs 34.6% for propofol), although the test for interaction was not statistically significant. The authors reported greater acute kidney injury and 5 instances of nephrogenic diabetes insipidus in the sevoflurane group. The adverse kidney effects could be due to elevated plasma fluoride (a by-product of sevoflurane metabolism) although the fluoride concentrations were not verified. There were also 2 instances of malignant hyperthermia, a known but normally extremely rare adverse effect of inhaled anesthetics during surgery.[12]

This is the largest study of inhalational sedation in ARDS, and it has many strengths. First, protocol fidelity was high, the 7-day duration maximized exposure to the intervention, the study population was appropriately enrolled, the trial was adequately powered, and the primary outcome was clearly defined. Second, the characteristics of the groups were largely similar at baseline, although the sevoflurane group had a higher proportion of female patients. Third, treatment measures outside of the trial protocol for ARDS, including ventilatory support, prone positioning, and extracorporeal membrane oxygenation, were similar between the groups. Fourth, the analysis was appropriate, with adjustment for stratification and per protocol and sensitivity analyses. Fifth, the pragmatic design and involvement of multiple centers improve the generalizability of results. Consideration for the variability in clinical

skill to deliver the intervention was detailed in the protocol with an educational package and the training was mandated and evaluated using an online-based evaluation module. Sixth, trialists had the foresight to collect biological samples for conducting mechanistic studies, the results of which will be reported in future articles.

However, there are some important caveats to some aspects of the trial design. A higher proportion of patients in the sevoflurane group received concomitant propofol between days 1 and 7; the protocol recommended early deep sedation and neuromuscular blockade for 48 hours before transition to lighter sedation. About 35% to 40% of the patients in both groups received continuous infusions of cisatracurium until day 6, a practice not routinely recommended in international guidelines. Consequently, it would appear that sedation interruption was only practiced in a small proportion of patients in both groups. There was lack of data on the inspired and expired concentrations of sevoflurane and titration of sevoflurane was based on clinical sedation scores.

Another point for consideration is the duration of the intervention. The duration of a general anesthetic with an inhalational agent is usually short, lasting only for a few hours. In the isoflurane trial, patients were exposed to the intervention for a maximum of 54 hours[9]; in the pilot trial by the study group investigators, the duration of exposure was 48 hours.[10] Sevoflurane is associated with cardiovascular depressant effects, nephrotoxicity, and formation of degradation products with carbon dioxide absorbent systems.[13] Whether the longer duration of exposure in the SESAR trial (7 days) accentuated these effects and was a critical factor in influencing outcomes is unknown.

The findings, while contributing substantially to the evidence base informing sedation strategies for patients with ARDS, also raise a number of important questions. First, the proportion of patients with refractory shock as a cause of death was higher in the sevoflurane group (15.6%) as compared with those assigned to propofol (9.5%). Patients in the sevoflurane group had consistently higher need for vasopressor or inotropic support evidenced by dosage data. This in conjunction with elevated serum lactate raises the possibility that sevoflurane contributed to severe circulatory shock. Second, the adverse effect of sevoflurane seemed to be more apparent in non–COVID-19 ARDS, raising the question of whether ARDS subphenotype matters for this intervention? Third, although the usage rates of corticosteroids in both groups were reported, information on dexamethasone dosage was missing, thus limiting the ability to interpret dexamethasone exposure in both groups. Higher doses of dexamethasone have been shown to be beneficial in both COVID-19 and non–COVID-19 ARDS.[14,15]

Sevoflurane, although established as a safe agent in anesthetic practice for decades, is still considered a relatively new intervention in critical care. The incorporation of new interventions in the management of critically ill patients, who often require complex respiratory and multiorgan support, can prove challenging, particularly in the face of a global pandemic and varying staff skill mix and nurse-patient ratios. Notably, this was a complex intervention, raising the possibility of a learning curve and, indeed, many centers enrolled just a few patients. The authors explored this possibility by repeating analyses with exclusion of the first 5 patients, but results did not differ. Analyses with adjustment for site were consistent. The results of this trial also raise the question as to why they differed from those of the pilot trial. Possible explanations include a shorter duration of administration of sevoflurane, fewer sites in the pilot trial, and a possible type I error.

Taken together, this is an elegant, pragmatic trial testing a challenging, innovative intervention in the sickest patients. With the caveats mentioned above, the investigators demonstrated that prolonged sevoflurane sedation resulted in worse outcomes as compared with propofol alone in patients with ARDS. These findings do not support the routine use of sevoflurane for sedation in critically ill patients with moderate to severe ARDS. Secondary analyses and mechanistic studies on biobanked specimens may provide further insights into understanding the direction of results and the heterogeneity in ARDS and inform the design of ongoing and future sedation trials.

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