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Inhalation Sedation in Subjects With ARDS Undergoing Continuous Lateral Rotational Therapy

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INTRODUCTION: Isoflurane has shown better sedation control and potential benefits in patients with ARDS compared to propofol or midazolam, but the practical use during continuous lateral rotational therapy remains unknown. We therefore compared isoflurane with propofol and midazolam regarding sedation depth (per the Richmond Agitation-Sedation Scale), opioid consumption, lung function, and hemodynamics in patients treated with continuous lateral rotational therapy. METHODS: 38 consecutive critically ill surgical subjects were retrospectively studied using a hospital database. All subjects suffered from ARDS and were treated with continuous lateral rotational therapy between May 2010 and September 2013. Nineteen subjects were sedated with propofol or midazolam and compared with 19 subjects sedated with isoflurane using the AnaConDa-system. RESULTS: Isoflurane sedation resulted in significantly lower Richmond Agitation-Sedation Scale scores compared with propofol or midazolam. Despite deep isoflurane sedation, opioid consumption could be significantly reduced. Spontaneous breathing was possible in 90% of the subjects on isoflurane sedation compared with 16% of the subjects sedated with propofol or midazolam. The difference between peak inspiratory pressure and PEEP was significantly decreased after 24 h of isoflurane sedation. Oxygenation (P_{aO_2}/F_{IO_2}) improved in both groups. Hemodynamics and need for vasopressor therapy were comparable between groups. CONCLUSIONS: This study supports the feasibility of isoflurane sedation using continuous lateral rotational therapy.
Key words: isoflurane; sedation; intensive care unit; Anaconda; Rotorest; acute respiratory distress syndrome; continuous lateral rotational therapy. [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Patients suffering from ARDS require invasive positive-pressure ventilation as well as some kind of positioning therapy. The S2e German guideline recommends semi-recumbent positioning for all ventilated patients, and prone positioning for those with severe oxygenation failure (P_{aO_2}/F_{IO_2} below 150 mm Hg).[1] If prone positioning seems contraindicated, as is often the case in patients with multiple trauma or after abdominal surgery with open abdomen or increased intra-abdominal pressure, continuous lateral rotational therapy is recommended as an alternative. Recent data also point to possible advantages of the early use of continuous lateral rotational therapy in patients with cardiogenic shock requiring prolonged ventilator therapy[2] or those with severe chest trauma to reduce pulmonary complications.[3]

Continuous lateral rotational therapy to maximal angles in awake patients represents a frightening experience and may cause motion sickness and vomiting. Therefore, deep sedation is often used. Current German and Spanish sedation guidelines recommend sedation using an inhaled anesthetic such as isoflurane as an alternative to intravenous sedation, especially when deep sedation is indicated.[4,5] In addition, isoflurane has bronchodilatory effects[6,7] and lung-protective

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properties,[8] which may be of benefit in patients with ARDS undergoing continuous lateral rotational therapy.[9]

The AnaConDa system (Sedana Medical, Uppsala, Sweden), commercially available in Europe and Canada, can be used to deliver inhaled anesthetics via common intensive care ventilators. The device is connected between the y-piece of the breathing circuit and the endotracheal tube. Liquid isoflurane is continuously infused by a syringe pump into the device, where it evaporates on the surface of a porous evaporator rod; 90% of exhaled isoflurane is retained by an anesthetic reflector and resupplied to the patient during the next inspiration.[10-12]

The use of isoflurane sedation in ARDS patients treated with continuous lateral rotational therapy is relatively novel and raises several safety questions. Given that isoflurane is administered via inhalation, the pharmacokinetics are uncertain when given in patients with ARDS who have poor lung function. In addition, the influence on pulmonary function, hemodynamics, and opioid consumption in patients with ARDS who require continuous lateral rotational therapy is unknown. Therefore, we report our experience with a consecutive cohort of 19 subjects with ARDS undergoing continuous lateral rotational therapy with isoflurane sedation. Moreover, we compared these subjects with 19 subjects sedated via the intravenous route using propofol or midazolam, focusing on the Richmond Agitation-Sedation Scale (RASS) score, opioid consumption, lung function, hemodynamics, and outcome. We hypothesized that, despite deep sedation, patients sedated with isoflurane would more often breathe spontaneously.

QUICK LOOK

Current knowledge

The AnaConDa system can be used to administer volatile anesthetics to critically ill patients using common ICU ventilators. Inhaled sedation with isoflurane is increasingly used by some ICUs in Europe and Canada as an alternative to intravenous sedation with propofol or midazolam, especially when deep sedation is indicated. Possible advantages include better control of sedation depth, shorter awakening times, and the possibility to reduce opioid use.

What this study adds to our knowledge

This paper describes the safe use of isoflurane in subjects with severe ARDS undergoing continuous lateral rotational therapy. Spontaneous breathing was facilitated despite deep sedation. In this small retrospective study, there were no significant differences in hemodynamics or outcome compared to intravenous sedation.

Methods

This retrospective case analysis was approved by the local ethics committee (Saarland Medical Chamber, Saarbruecken, Germany). From the hospital information system (SAP Healthcare, Walldorf, Germany), all patients with continuous lateral rotational therapy were identified retrospectively. This cohort of consecutive subjects was treated between May 2010 and September 2013 in the surgical ICU at the Saarland University Medical Center in Homburg, Germany.

The indication to use continuous lateral rotational therapy was severe oxygenation failure ($P_{aO_2}/F_{IO_2} < 150$ mm Hg) with contra-indications for prone positioning. These included use of external fixators at the pelvis or several extremities, or severely distended, open abdomen with negative pressure wound therapy. In some subjects with severe chest trauma, continuous lateral rotational therapy was used early to reduce pulmonary complications. The clinical decision to discontinue continuous lateral rotational therapy was made during daily pauses of 60 min, looking at oxygenation and stabilization of pulmonary function.

For continuous lateral rotational therapy we used a special bed that rotated on its long axis (Rotorest, ArjoHuntleigh, Malmö, Sweden). The subject's head, torso, and extremities were supported on all sides with adjustable padded attachments and secured with belts according to the instructions of the manufacturer. The bed turns as much as 62 degrees to both sides. We used full-angle rotation without stopping on any side. Once daily, continuous lateral rotational therapy was paused with the patient in a recumbent position to allow physical examination, chest radiographs, and nursing care.

Group Protocols

The treatment of all subjects depended on the disease process and not on the mode of sedation. Isoflurane sedation has been available since June 2011. Before that date, all patients received propofol or midazolam for sedation. Since June 2011, the decision to use isoflurane for sedation depended primarily on the availability of the equipment: only one patient could be sedated with AnaConDa at a time.

Artificial Ventilation

All subjects were ventilated with an Evita 4 ventilator (Dräger Medical, Lübeck, Germany) in pressure-controlled mode (biphasic positive airway pressure). The inspiratory pressure was adjusted to keep the tidal volumes at 6–8 mL/kg ideal body weight. Whenever spontaneous breathing activity was noted, the pressure support mode

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was used. We used closed endotracheal suctioning in all subjects (Optiflo, Dahlhausen Medizintechnik, Köln, Germany). For subjects sedated with isoflurane, the gas outlet of the ventilator was connected to a FlurAbsorb anesthetic gas filter (Sedana Medical).

Isoflurane Group

The AnaConDa system and the Vamos gas monitor (Dräger Medical) were set up as prescribed by the manufacturer. Liquid isoflurane was delivered by a syringe pump (Perfusor, Braun Melsungen, Germany). After priming the system, isoflurane was started at a rate of 5 mL/h and adjusted according to the clinical condition (hemodynamic stability, RASS scores −4 to −5) and the end-tidal anesthetic concentration, which was continuously monitored. The infusion rate needed to keep the subject sedated also depends on the minute ventilation, which may change with time,[10] the nurses titrated the infusion rate. If rates > 8 mL/h were needed, a physician was informed. When starting inhalation sedation, previously used intravenous sedation was stopped without overlap.

In 10 subjects, isoflurane sedation was started immediately, in 4 subjects it was started within 24 h, and in 5 subjects it was started > 24 h after initiation of continuous lateral rotational therapy. Data were recorded at the start of isoflurane sedation, as well as at 6 and 24 h after.

Intravenous Group

Previously used intravenous sedation with either propofol or midazolam was continued unchanged. For a fair comparison of both groups, the observation times were comparable. Therefore, to compare the same time points with regard to the initiation of continuous lateral rotational therapy, subjects were matched by a study nurse blinded to the data and to the purpose of the study: 10 subjects sedated intravenously were randomly selected and assigned to the 10 subjects in whom isoflurane was started immediately after continuous lateral rotational therapy. The remaining patients were randomly matched, and data from the same time points with regard to the start of continuous lateral rotational therapy were collected.

Data Source and Measurements

Data were extracted from the ICU patient data management system (Copra, Version 5, Copra System, Berlin, Germany). Subject' characteristics, Simplified Acute Physiology II (SAPS II) scores, comorbidities, diagnostic data, drug doses, RASS scores, and details on continuous lateral rotational therapy were entered manually into this system by physicians and nurses. Vital parameters such as heart rate, invasive mean arterial pressure, blood gases, and ventilatory parameters were automatically transferred to this system and stored after having been checked by the nurses for plausibility.

Table 1. Subjects' Medical History

	Propofol/Midazolam	Isoflurane	*P*
Male	12 (63)	14 (74)	.50
Age, y	56.3 ± 21.4	48.9 ± 16.9	.23
Body mass index, kg/m^2	25.0 ± 4.7	28.3 ± 5.7	0.062
Comorbidity			
Coronary heart disease	1 (5)	1 (5)	>.99
Stroke	0	1 (5)	.31
Renal failure	1 (5)	4 (21)	.15
COPD	2 (11)	3 (16)	.63
Diabetes	2 (11)	1 (5)	.55
Surgery			
Emergency	9 (47)	14 (74)	.10
Abdominal surgery	15 (79)	10 (53)	.09
Bone surgery	4 (21)	6 (32)	.46
Before Rotorest			
Multiple trauma	4 (21)	7 (37)	.28
Pneumonia or sepsis from other causes	17 (90)	17 (90)	>.99
Renal replacement therapy	11 (58)	11 (58)	>.99

n = 19 for both groups. Data are mean ± SD or *n* (%).

Data Analysis

Continuous variables are expressed as mean and SD; categorical variables are presented as absolute and relative frequencies, respectively. Categorical variables in the isoflurane group and the intravenous group were compared using chi-square tests. Continuous variables were compared using Student *t* tests (or Welch *t* tests when variance was inhomogeneous). Data analysis was performed using SPSS Statistics 19 (IBM, Ehningen, Germany). Statistical significance was accepted at a 2-sided significance level of $\alpha = 0.05$. Figures were made with GraphPad Prism 5.0 (GraphPad Software, San Diego, California).

Results

During the observation period, a total of 38 subjects were treated with continuous lateral rotational therapy and sedation. All subjects were studied and followed for hospital stay: 19 in the intravenous and 19 in the isoflurane group.

Subjects' medical histories prior to continuous lateral rotational therapy were not significantly different between groups (Table 1). Causes of ARDS were pneumonia and sepsis from other sources of infection after surgical procedures or multiple trauma. The SAPS II scores were

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43.4 ± 14.8 in the intravenous and 40.2 ± 9.6 in the isoflurane group ($P = .44$) at initiation of continuous lateral rotational therapy (Table 2). Reasons for continuous lateral rotational therapy were severe oxygenation failure or severe chest trauma. In all subjects, continuous lateral rotational therapy was started within 24–48 h of meeting clinical criteria. Heart failure was excluded using transesophageal or thoracic echocardiography.

Sedation

Both groups were deeply sedated after initiation of continuous lateral rotational therapy. Muscular paralysis was not used during the observation period. After isoflurane sedation was started, deep sedation (RASS −4 to −5) was readily achievable and RASS was significantly lower after 24 h compared with the intravenous group (Fig. 1). Despite low RASS Scores, all subjects in both groups showed reactions (coughing) to endotracheal suctioning. The dose of isoflurane was 3–10 mL/h with end-tidal concentrations ranging from 0.5 to 0.8 mL/dL. No technical problems during isoflurane sedation were encountered. During the observation period, slightly more dose changes were performed in the isoflurane group than in the intravenous group (2.7 ± 1.9 vs 1.9 ± 1.8, not significant). Opioid consumption was significantly decreased in patients with isoflurane after 6 and 24 h (Fig. 1, Table 2).

Lung Function

Interestingly, after 24 h of isoflurane sedation, 90% of the subjects were able to breathe spontaneously during deep sedation, compared to only 15% in the intravenous group (Table 2). In addition, in isoflurane-sedated subjects, Δ P (peak inspiratory pressure − PEEP) could be significantly reduced compared to propofol/midazolam, whereas tidal volumes remained unchanged (Fig. 1). The P_{aO_2}/F_{IO_2} ratio improved significantly in both groups over time (Table 2).

Hemodynamics

Inhalation sedation was not associated with hemodynamic instability (Fig. 2). The norepinephrine dose, mean arterial pressure, and heart rate were comparable between the groups. During 24 h of isoflurane sedation, no significant changes were observed.

Outcome

There were no significant differences in time on the ventilator, length of stay, or mortality (Table 3).

Table 2. SAPS II Score, Sedative Drugs, and Ventilator Parameters Before and During Study Sedation

	Propofol/Midazolam $n = 19$	Isoflurane $n = 19$	P
SAPS II, points			
Before	43.2 ± 15.2	40.2 ± 9.6	.47
6 h	41.4 ± 14.9	39.2 ± 9.8	.61
24 h	42.6 ± 13.8	35.7 ± 10.2	.10
Propofol, mg/kg/h	n = 15	n = 16	
Before	0.83 ± 0.39	0.80 ± 0.43	.83
6 h	0.87 ± 0.42	0 ± 0	ND
24 h	0.10 ± 0.46	0 ± 0	ND
Midazolam, mg/kg/h	$n = 4$	$n = 3$	
Before	0.07 ± 0.03	0.11 ± 0.02	0.060
6 h	0.07 ± 0.03	0 ± 0	ND
24 h	0.10 ± 0.05	0 ± 0	ND
Isoflurane, mL/h			
Before	0 ± 0	0 ± 0	ND
6 h	0 ± 0	5.2 ± 2.1	ND
24 h	0 ± 0	4.9 ± 1.7	ND
Remifentanil, μg/kg/min	n = 14	n = 16	
Before	0.22 ± 0.09	0.19 ± 0.10	.39
6 h	0.23 ± 0.10	0.10 ± 0.04*	.007
24 h	0.25 ± 0.09	0.09 ± 0.04*	< .001
Sufentanil, μg/kg/h	$n = 5$	$n = 3$	
Before	0.68 ± 0.59	0.46 ± 0.66	.64
6 h	0.68 ± 0.58	0.29 ± 0.45	.20
24 h	0.52 ± 0.55	0.29 ± 0.45	.38
Spontaneous breathing			
Before	3 (16)	2 (11)	.64
6 h	3 (16)	12 (63)	.003
24 h	3 (16)	17 (90)	< .001
PEEP, cm H_2O			
Before	13.5 ± 2.7	12.2 ± 2.8	.16
6 h	12.7 ± 3.2	13.9 ± 3.2	.26
24 h	12.7 ± 3.1	13.2 ± 3.1	.59
Breathing frequency, breaths/min			
Before	24.6 ± 5.9	20.2 ± 5.4	.026
6 h	23.5 ± 5.7	22.4 ± 5.8	.56
24 h	24.7 ± 5.4	22.0 ± 6.6	.20
Tidal volume, mL			
Before	499 ± 134	580 ± 175	.12
6 h	525 ± 119	606 ± 204	.17
24 h	566 ± 140	531 ± 167	.50
Minute volume, L			
Before	12.4 ± 4.5	11.6 ± 4.4	.61
6 h	12.8 ± 4.7	13.6 ± 5.7	.52
24 h	13.5 ± 4.2	11.6 ± 4.8	.22
P_{aO_2}/F_{IO_2}, mm Hg			
Before	172 ± 63	157 ± 71	.48
6 h	165 ± 77	182 ± 103	.58
24 h	199 ± 73	195 ± 83	.85
P_{aCO_2}, mm Hg			
Before	53 ± 10	51 ± 10	.52
6 h	53 ± 10	56 ± 13	.37
24 h	52 ± 10	58 ± 14	.17

Data are mean ± SD or *n* (%).
ND = not done
SAPS = Simplified Acute Physiology Score II
P_{aCO_2} = arterial partial pressure of carbon dioxide

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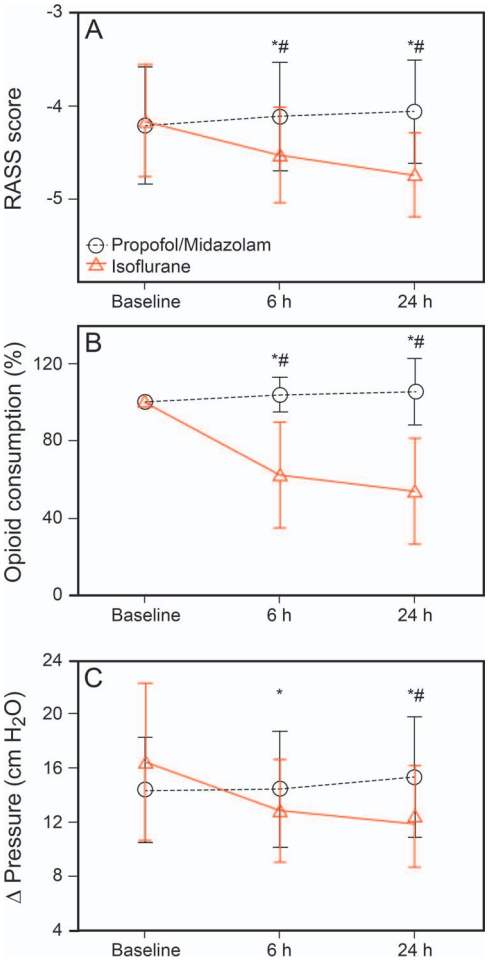

Fig. 1. Richmond Agitation-Sedation Scale (RASS) score (A), opioid consumption (B), and lung function (C); before and during isoflurane sedation compared with propofol/midazolam. Data are shown as mean ± SD. * $P < .05$ compared to baseline, # $P < .05$ compared to propofol/midazolam.

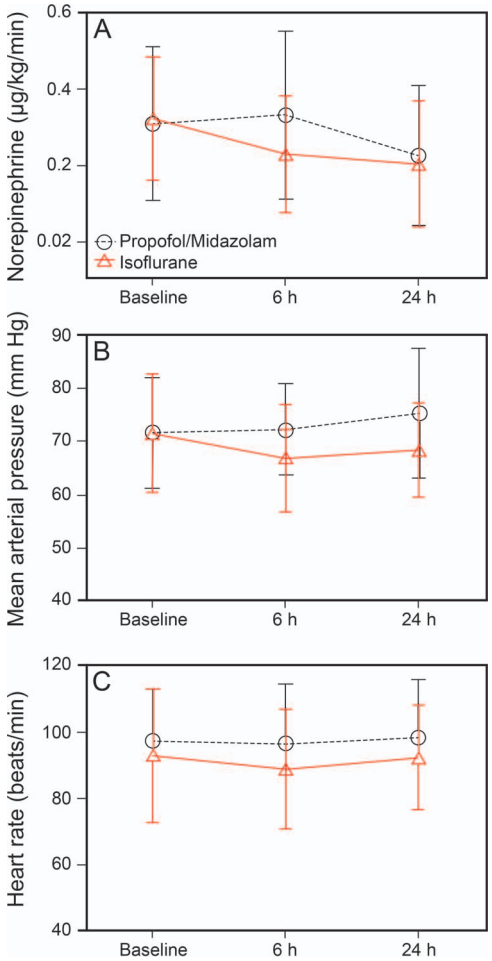

Fig. 2. Norepinephrine dose and hemodynamic data; before and during isoflurane sedation compared with propofol/midazolam. Data are shown as mean ± SD.

Discussion

In this study we describe the successful use of isoflurane sedation with the AnaConDa system in 19 subjects being treated with continuous lateral rotational therapy for respiratory failure. This strategy was feasible, with theoretical advantages including bronchodilation,[6,7] cardiovascular[13] and lung-protective effects,[14,15] good control of the level of sedation,[16,17] and the ability to achieve deep sedation. We compared 19 isoflurane-sedated subjects with 19 subjects sedated via the intravenous route using propofol or midazolam and observed significantly decreased opioid consumption, deeper sedation, more spontaneous breathing, a decreased Δ P (peak inspiratory pressure − PEEP), and hemodynamically stable conditions after 24 h isoflurane versus propofol/midazolam.

While receiving isoflurane, all subjects also reacted to endotracheal suctioning despite RASS scores of −4 to −5.

Table 3. Outcomes

	Propofol/ Midazolam	Isoflurane	*P*
Invasive ventilation, h	618 ± 503	465 ± 230	.26
Length of stay, d			
In Rotorest	6.4 ± 5.4	7.7 ± 5.0	.44
In ICU	36 ± 33	30 ± 14	.48
In hospital	51 ± 37	45 ± 27	.60
Mortality during continuous lateral rotational therapy	4 (21)	2 (11)	.39

$n = 19$ for both groups. Data are mean ± SD or n (%).

Despite deep sedation, opioid administration could be significantly reduced after initiating isoflurane sedation. This observation is in line with previous studies. In the first randomized, controlled trial on inhalation sedation with the AnaConDa system, morphine consumption tended to

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be lower during sedation with isoflurane versus with midazolam (2.7 vs 4.2 mg/h).[17] In a crossover trial including 17 intensive care subjects, sevoflurane administered without opioid analgesia was equally effective in achieving the sedation targets compared to propofol-remifentanil.[18] In another randomized, controlled trial, pain scores after stop of sedation as well as morphine consumption 24 h post-extubation were significantly lower after sevoflurane compared to propofol or midazolam sedation. The authors discussed an antihyperalgesic effect of volatile anesthetics.[19]

Interestingly, during deep isoflurane sedation 90% of the subjects in our study were breathing spontaneously augmented with 5–18 cm H_2O pressure support. This was previously described during use of inhalation sedation.[18,20,21] It can be assumed that augmented spontaneous breathing may recruit lung tissue in dependent areas, which could be of benefit if sufficient PEEP is used to prevent cyclic collapse of alveoli (atalectrauma).[22]

Also of note, Δ P was significantly decreased after initiating isoflurane sedation. Possible mechanisms for this effect include purposeful activity of the diaphragm and improved lung compliance due to anti-inflammatory properties of volatile agents.[8,23] Although some recommend muscular paralysis during the first 48 h in patients with severe ARDS,[24] we did not use muscular relaxants because they interfere with monitoring the depth of sedation clinically and preclude spontaneous breathing.

Care must be taken when initiating isoflurane sedation because isoflurane, like propofol, is a potent vasodilator and may cause hemodynamic instability, especially at higher doses. Isoflurane was therefore started at a constant infusion rate, with concentrations building up slowly, and previously used intravenous sedation was stopped without overlap. As most patients in the isoflurane group were previously sedated with propofol, we did not notice a decrease in arterial pressures or an increase in vasopressor use. Also, there was no significant difference in hemodynamics between isoflurane and intravenous sedation.

Because of the high internal dead space of 100 mL and some CO_2 reflection, CO_2 removal is impaired with the AnaConDa device.[17,20,25] We noted a slight increase in P_{aCO_2}, but this was not significant. Consequently, tidal volumes $>$ 350 mL are normally recommended, which may preclude the use of this device when low-volume lung-protective ventilation strategies are used in smaller patients. In our study, all subjects had tidal volumes $>$ 350 mL with sufficient elimination of CO_2 in both groups. However, a reduction in device dead space of the AnaConDa system would be desirable.

In all study subjects, we used closed endotracheal suctioning to allow removal of respiratory secretions without loss of airway pressure and to reduce workplace contamination with isoflurane. There were no problems with secretions in these subjects, although copious secretions may interfere with proper function of the AnaConDa device.

Isoflurane-sedated subjects had significantly lower RASS scores, which suggest deeper sedation. It was shown that deep intravenous sedation is associated with an increase in mortality.[26-28] However, one previous study suggests that the mortality of long-term ventilated critically ill subjects sedated with isoflurane may be lower than that of patients sedated intravenously with propofol or midazolam.[29] In line with this, in our study there was no increased mortality in subjects sedated deeply with isoflurane (11%) compared to subjects sedated with propofol/midazolam at higher RASS scores (21%, $P = .37$). Nevertheless, our study was not powered to detect differences in mortality. Further multi-center, randomized, controlled trials are needed to investigate the possible benefits of sedation with isoflurane in patients with ARDS.

Conclusion

We found that sedation with isoflurane was successful in critically ill subjects on continuous lateral rotational therapy. Subjects required less opioids and were able to breathe spontaneously while deeply sedated compared to sedation with propofol/midazolam. No adverse events were noted related to isoflurane sedation.

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