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Limiting Sedation for Patients with ARDS – Time to Wake Up

Faraaz Ali Shah, MD¹, Timothy D. Girard, MD, MSCI², and Sachin Yende, MD, MS^{2,3}

¹Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh, Pittsburgh, USA

²CRISMA Center, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, USA

³Veterans Affairs Pittsburgh Healthcare System, University Drive C, Pittsburgh, USA

Abstract

Purpose of Review—Critically ill patients with acute respiratory distress syndrome (ARDS) may require sedation in their clinical care. The goals of sedation in ARDS patients are to improve patient comfort and tolerance of supportive and therapeutic measures without contributing to adverse outcomes. This review discusses the current evidence for sedation management in patients with ARDS.

Recent Findings—Deep sedation strategies should be avoided in the care of patients with ARDS because deep sedation has been associated with increased time on mechanical ventilation, longer ICU and hospital length of stay, and higher mortality in critically ill patients. Adoption of protocol-based, light-sedation strategies are preferred and improve patient outcomes. Although the optimal sedative agent for ARDS patients is unclear, benzodiazepines should be avoided due to associations with oversedation, delirium, prolonged intensive care unit and hospital length of stay, and increased mortality. Minimizing sedation in patients with ARDS facilitates early mobilization and early discharge from the intensive care unit, potentially aiding in recovery from critical illness. Strategies to optimize ventilation in ARDS patients, such as low-tidal volume ventilation and high positive end-expiratory pressure (PEEP) can be employed without deep sedation; however, deep sedation is required if patients receive neuromuscular blockade, which may benefit some ARDS patients. Knowledge gaps persist as to whether or not prone positioning and extracorporeal membrane oxygenation (ECMO) can be tolerated with light sedation.

Summary—Current evidence supports the use of protocol-based, light-sedation strategies in critically ill patients with ARDS. Further research into sedation management specifically in ARDS populations is needed.

Keywords

acute respiratory distress syndrome; sedation; outcomes

Corresponding Author: Sachin Yende, MD, MS, VA Pittsburgh Healthcare System, University Drive C, Room 2A124, Pittsburgh, PA 15240, USA, yendes@upmc.edu.

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None.

Introduction

Many patients with moderate or severe acute respiratory distress syndrome (ARDS) will require sedation and analgesia in the setting of mechanical ventilation. Sedation management is an important component of the care of critically ill patients and a modifiable factor influencing their outcomes. While sedation can improve comfort for critically ill patients, some sedation strategies can have negative consequences including prolonged duration of mechanical ventilation and increased risk of delirium. This review provides an overview of recent advances to minimize sedation and focuses on the benefits of limiting sedation, weaning strategies and protocols, and the relationship between sedation strategies and delirium.

Although very few trials of sedation management in the ICU limited enrollment to include only patients with ARDS, many of the key randomized trials of sedation management published in the last two decades included a substantial proportion of patients with ARDS (Table 1). We review herein the evidence from these trials to provide guidance in improving care delivered to critically ill patients with ARDS.

Minimizing Sedation

The goals of sedation in the intensive care unit are to keep the patient comfortable enough to tolerate treatment and, occasionally, to promote patient safety.^{5,6} In patients with ARDS, sedation is used to improve patient tolerance of mechanical ventilation, reduce discomfort, and, in some cases, to improve patient-ventilator synchrony.⁷ Sedation practices have changed dramatically in the past three decades. In the 1980s, deep sedation was common to provide comfort and limit memory of the critical illness. However, several clinical trials since the 1990s have shown that oversedation is common in the ICU and contributes to adverse outcomes.⁸ A prospective multi-center Australian cohort study demonstrated that deep sedation within the first 48 hours of ICU admission was predictive of delayed time to extubation and increased risk of in-hospital and 180-day mortality in a mixed ICU population. [Figure 1]⁹ A subsequent Brazilian prospective cohort study similarly associated early deep sedation with increased time on mechanical ventilation, risk of having a tracheostomy, and higher mortality, and furthermore demonstrated that the effects of deep sedation on mortality were independent of severity of ARDS illness.¹⁰

Strategies to minimize deep sedation have beneficial effects in critically ill patients. A landmark randomized trial in 1999 found that protocol-directed, nursing-led sedation decreased duration of mechanical ventilation, ICU and hospital length of stay, and need for tracheostomy when compared with usual care.¹¹ A second landmark trial in 2000 found that daily interruptions of continuous sedation reduced total amount of sedative delivered and subsequently reduced time on mechanical ventilation by more than 2 days and ICU length of stay by 3.5 days compared with usual care.¹ Later, a multi-center randomized controlled trial compared paired sedation interruption and spontaneous breathing trials with usual care and demonstrated that the paired protocol minimized deep sedation and reduced one-year mortality in critically ill patients. [Figure 2]³ Opponents of minimizing sedation raised the

possibility of increased risk of neuropsychological outcomes, but several studies have shown that patients who received lighter sedation do not experience these adverse effects.^{8,12,13} Furthermore, some protocols for critically ill patients utilize a “no sedation” approach using analgesics alone with no or intermittent sedative use, an approach which in small studies has decreased time on mechanical ventilation compared with usual care.^{14,15}

One of the key benefits to limiting sedation use in patients with ARDS may be improved ability to participate in early mobilization and rehabilitation.¹⁶ Early mobilization is particularly important in patients with ARDS as over 50% of survivors suffer from deficits in physical and cognitive function that persist for years beyond the inciting event.^{12,17–21} Several clinical trials have shown that early mobilization in both medical and surgical critically ill patients is safe and associated with increased ventilator-free days and improved physical function at hospital discharge.^{22–25} Early mobilization is limited by use of deep sedation and development of delirium, which can be minimized through the use of scale-based targeted light sedation is implemented early on.²⁶

After reviewing this literature in 2013, the Society of Critical Care Medicine (SCCM)’s Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit recommended using a light rather than deep sedation strategy for critically ill patients.²⁷ Similarly, new guidelines on liberation from mechanical ventilation published jointly by the American College of Chest Physicians and the American Thoracic Society recommend using a sedation protocol to minimize sedation of mechanically ventilated ICU patients.²⁸

Balanced against the recommendation for light sedation is the occasional need for deep sedation during advanced therapies for severe ARDS. A number of studies have shown that deep sedation is not required for patients to tolerate the low tidal volume ventilation^{29–31} or high PEEP strategies^{32,33} that are often employed for management of ARDS. However, deep sedation is required in patients with ARDS who receive neuromuscular blockage to ensure patients do not consciously experience paralysis.^{34,35} Neuromuscular blockage is sometimes used in severe ARDS based on results of a multicenter trial in France that showed improved mortality with 48 hours of neuromuscular blockage in patients who have severe hypoxemia ($\text{PaO}_2/\text{FiO}_2$ ratio < 150) early during their ARDS.³⁶ A large, multicenter trial (NCT02509078) is now underway in the United States (US) to rigorously test whether early neuromuscular blockade results in better outcomes for patients with severe ARDS compared to current standard of care approaches, including light sedation. It is important to recognize that the French trial used a double-blind design, thus patients in the control arm also received deep sedation similar to patients in the intervention arm, an approach some have criticized as harmful to patients in the control arm. In contrast, the Prevention and Early Treatment of Acute Lung Injury (PETAL) investigators conducting the ongoing US trial are not blinded to the intervention and light sedation is recommended for patients in the control group.

Management of sedation for patients who receive other interventions in ARDS, such as prone positioning and extracorporeal membrane oxygenation (ECMO), remains unclear. For instance, compared to ARDS patients who do not receive ECMO, patients receiving ECMO

may need higher sedation to tolerate the invasiveness of the procedure, to compensate for sedatives consumed by the ECMO circuit itself,³⁷ and because patients who receive ECMO tend to be younger and have higher illness severity.^{38,39} Whether higher sedation is actually necessary for these patients is not known. Minimizing sedation in these patients should remain an important goal to minimize delirium, increase patient mobilization, and optimize patient recovery.⁴⁰

Weaning Sedation

Two early landmark trials in sedation management demonstrated a benefit in both daily sedation awakening and in paired sedation interruption and spontaneous breathing trials in decreasing overall sedation requirements, decreasing time on mechanical ventilation, and decreasing ICU length of stay in critically ill patients when compared to usual care.^{1,3} Recent meta-analyses examining the effects of daily sedation interruption trials have not demonstrated the same magnitude of benefit in reducing time on mechanical ventilation or ICU length of stay.^{41,42} There are several possible explanations for these findings. First, studies suggested that the benefit of daily sedation interruption is only realized when the overall amount of sedatives received by critically ill patients is reduced, and not all trials achieved this goal in patients randomized to daily interruption of sedatives.⁴ For example, patients in the daily interruption of sedatives group of the SLEAP trial received more midazolam and fentanyl boluses than those managed without daily interruption of sedatives, and the trial found no difference in outcomes between groups. Second, the benefits of daily interruption of sedatives noted in early trials may not be observed in more recent trials due to changes in sedation practices over time affecting the management of sedation in the control arm. For instance, guidelines now recommend light sedation goals and advocate for the use of validated sedation scales, such as the Richmond Agitation-Sedation Scale, which help limit sedative and analgesia use. Thus the standard of care has changed over time and may have led to use of lighter sedation in the control arm in more recent clinical trials compared to older studies.^{27,43–46} Finally, isolating the effects of daily sedation interruption trials in clinical practice is challenging as daily awakening trials are now frequently bundled with other interventions to improve the quality of care delivered to critically ill patients. An example of a bundled quality care intervention includes the ABCDE Bundle (Awakening and Breathing Coordination of daily sedation and ventilator removal trials; Choice of sedative or analgesic exposure; Delirium monitoring and management; and Early mobility and exercise).^{47–49} The use of these evidence-based bundles, which starts with decreasing sedation use, has been associated with decreased delirium, decreased time on mechanical ventilation, and decreased ICU length of stay.^{50, 51} Thus, whether minimized via the use of daily interruption of sedatives or other protocolized approaches to minimizing sedation, one thing is clear—light (or even no) sedation results in better outcomes for mechanically ventilated ICU patients, including those with ARDS.

Type of Sedation

The 2013 SCCM Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit suggest using a non-benzodiazepine agent for sedation of mechanically ventilated ICU patients except when a benzodiazepine is indicated due to

seizure, alcohol or benzodiazepine withdrawal, or to ensure deep sedation and amnesia (e.g., during paralysis). Recent studies have confirmed that the use of benzodiazepines for sedation in critically ill patients is associated with increased delirium, increased hospital length of stay, increased time on mechanical ventilation, and increased intensive care unit hospitalization.^{2,52–54} A recent propensity-based analysis also suggested that benzodiazepine use in critically ill patients is associated with increased mortality, further strengthening the argument for relying on non-benzodiazepine agents, such as propofol or dexmedetomidine.⁵⁵ Benzodiazepines may still be considered in rare cases when patients develop side effects from other sedatives or when they have chronically been using benzodiazepines in the outpatient setting, but even in these cases an intermittent sedative approach can be considered and benzodiazepine use should be limited when possible.⁵⁶ While evidence for type of sedation for critically ill patients specifically with ARDS remains limited, results from these recent studies support starting initially with a non-benzodiazepine sedative agent.

Risks of Delirium

Delirium complicates up to 70%–80% percent of cases of ARDS and has been identified as an independent risk factor for increased hospital and ICU length of stay, increased mortality, and increased long-term cognitive impairment in survivors of critical illness.^{21, 57–63} The mechanisms linking delirium to adverse outcomes in ARDS remain unclear,^{64,65} and several recent studies have explored the potential role of sedation as an iatrogenic contributing factor.

A recent cohort study of adult ICU patients admitted with respiratory failure or shock prospectively assessed inpatient delirium and sedative use and examined risk factors associated with long-term cognitive impairment in survivors of critical illness. After adjusting for duration of delirium, which was found to be associated with development of long-term cognitive impairments in this study, sedative use was not an independent risk factor for long-term cognitive deficits.²¹ Given that heavy sedation, especially with benzodiazepines, has been consistently found to increase delirium risk, these findings do not rule out the possibility that heavy sedation plays a role in adverse long-term cognitive outcomes. Instead, they suggest that the patients with ARDS who are at highest risk for sedative-associated long-term cognitive impairment are those who develop persistent delirium when receiving sedatives. For reasons that have yet to be elucidated, some patients may be at higher risk for sedative-associated delirium than others. The SCCM guidelines recommend monitoring all ICU patients for delirium using either the Confusion Assessment Method for the ICU^{66, 67} or the Intensive Care Delirium Screening Checklist,⁶⁸ both of which have been validated in mechanically ventilated ICU patients, including those with ARDS. When delirium is identified, one change in management to consider is that of sedative choice.

One recent study suggested that 10% of mechanically ventilated ICU patients develop rapidly reversible delirium in the setting of sedation, whereas a larger proportion develop delirium that persists after cessation of sedatives. This study categorized patients into one of four groups: (1) no delirium, (2) rapidly reversible delirium associated with sedative use

which resolved when sedation was held, (3) persistent delirium where delirium did not improve when sedation was weaned, and (4) mixed delirium, which had characteristics of both rapidly reversible delirium and persistent delirium. Persistent and mixed delirium were associated with significantly worse ICU outcomes, whereas rapidly reversible delirium associated with sedation was associated with outcomes similar to those that had no delirium. Of note, benzodiazepine use was minimal in this study, and the rapidly reversible form of delirium was uncommon, such that this small study was underpowered to detect differences in outcomes in this group.⁶⁹

Optimal management of critically ill patients with delirium remains unclear but focuses on correcting the underlying illness and minimizing medications that could contribute to delirium.⁷⁰ Two recent randomized, placebo-controlled trials showed that, in critically ill patients with agitation, dexmedetomidine reduces delirium and decreases time to successful extubation.^{71,72} Additionally, a meta-analysis compared the efficacy of dexmedetomidine to other sedative agents and showed that dexmedetomidine is associated with less delirium.⁷³ The role of antipsychotic medications, common in the treatment of hospitalized patients with delirium that are not in the ICU, remains unclear as few placebo-controlled, randomized clinical trials have been performed to assess the effects of typical or atypical antipsychotics in critical care settings.^{74–76} A recent clinical trial exploring the role of haloperidol to prevent and treat the occurrence of delirium found that the regular use of haloperidol did not affect number of days with delirium or survival in critically ill patients.⁷⁷ The results of these clinical trials emphasize the need for further research into the mechanisms and management of delirium in critically ill patients but do not suggest that the deleterious effects of delirium are influenced by sedative use.

Immune Effects of Sedation

The benefits of limiting sedation may extend beyond avoiding oversedation, facilitating early mobilization, and reducing the duration of mechanical ventilation, ICU stay, and delirium. Sedative agents have been suggested to have broad immune effects. For example, studies in rats have shown that propofol may impair neutrophil phagocytosis and lipopolysaccharide-induced macrophage Th1 cytokine response.^{78,79} Similarly, dexmedetomidine may have anti-inflammatory effects and improve macrophage function.^{80, 81} Some of these immune effects may be beneficial in patients with sepsis, the most common cause of ARDS. There is increasing recognition that sepsis is a heterogeneous condition and includes patients who have increased inflammation and are immunosuppressed.^{82,83} Thus, understanding the immunomodulatory effects of sedative agents on ARDS will be challenging and will be an important area for future studies.

Conclusion

Sedation management is an important component in the care of critically ill patients with ARDS. The goals of sedation should be to reduce discomfort and improve patient tolerance of mechanical ventilation and other advanced therapies for ARDS, while avoiding deep sedation when possible. Sedation protocols should prioritize non-benzodiazepine regimens and utilize daily sedation weaning and/or protocol based sedation algorithms to target light

levels of sedation titrated using validated scales. Improved sedation management in critically ill patients is associated with decreased delirium and improved early mobilization which may help improve outcomes in patients with ARDS. Further research into the management of sedation and mechanisms by which specific sedation strategies would improve outcomes, specifically in patients with ARDS, is needed.

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Key Phrases

- This review highlights recent advances in sedation management in critically ill patients with the acute respiratory distress syndrome (ARDS).
- Current evidence supports the use of protocol-based, light-sedation strategies; many therapeutic interventions for ARDS, including high PEEP and low-tidal volume ventilation, can be achieved without deep sedation.
- Further research in sedation use specifically in ARDS populations is needed.
- Benefits of minimizing sedation in ARDS patients include decreasing delirium, facilitating early mobilization, and reducing ICU and hospital length of stay, and potentially improving mortality and long term recovery.

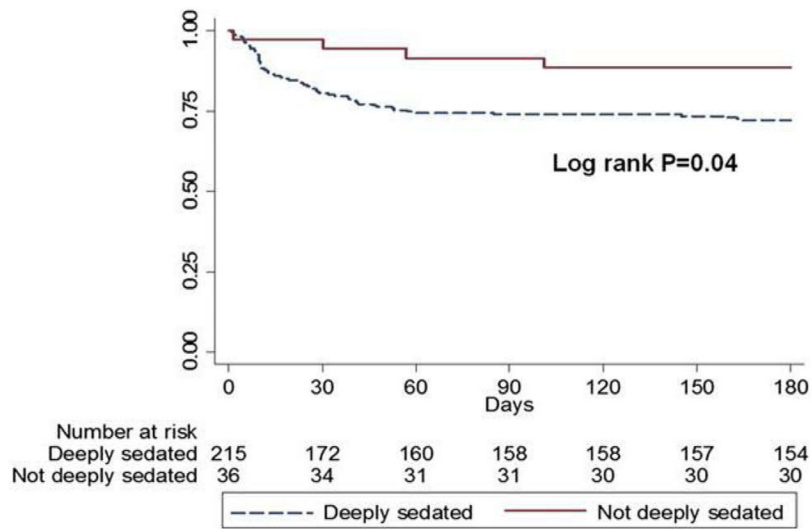


Figure 1. Observational cohort study by Shehabi et al⁹ demonstrating that deep sedation is associated with worse survival at 3 months in mechanically ventilated critically ill patients. (With permission from 9)

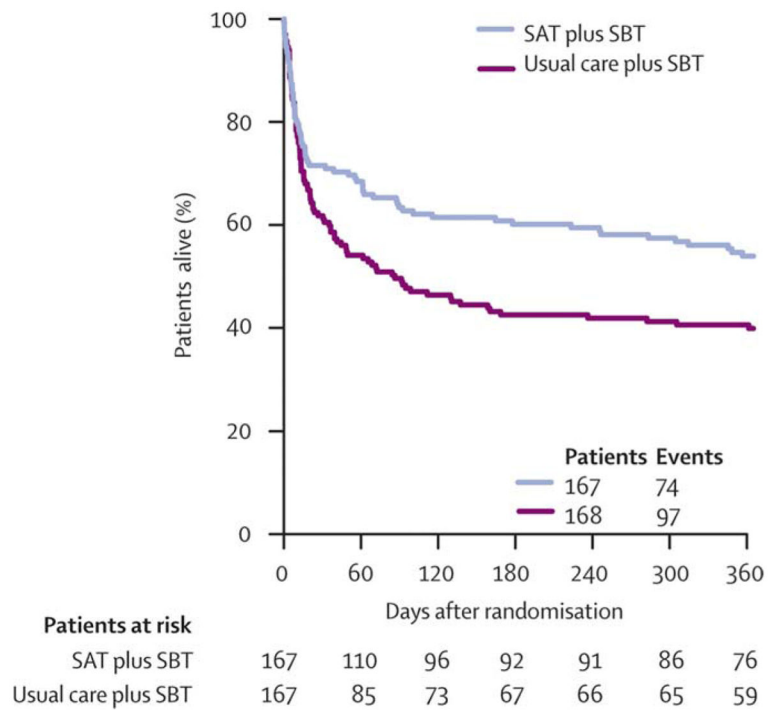


Figure 2. Randomized controlled clinical trial by Girard et al³ demonstrating that pairing spontaneous awakening trials (SAT) and spontaneous breathing breathing trials (SBT) in critically ill patients increased 1 year survival. (with permission from 3)

Table 1

Enrollment of Patients with Acute Respiratory Distress Syndrome in Clinical Studies of Sedation

Author	Year	Clinical Study	Patients with ARDS/Total Patients in Study (%)
Kress et al ¹	2000	RCT of daily sedation interruption versus usual care	35/150 (23.33%)
Pandharipande et al ²	2007	RCT of continuous dexmedetomidine versus midazolam	39/103 (37.86%)*
Girard et al ³	2008	RCT of paired daily sedation interruption and spontaneous breathing trials versus usual care	166/355 (49.55%)*
Mehta et al ⁴	2012	RCT of protocolized sedation versus protocolized sedation with daily sedation interruption	23/65 (35.38%)**

* - Includes patients with ARDS and with sepsis

** - Includes patients with ARDS and with pneumonia

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