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Evolving targets for sedation during mechanical ventilation

Steven D. Pearson, **Bhakti K. Patel**

Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago, Chicago, Illinois, USA

Abstract

Purposes of review—Critically ill patients frequently require mechanical ventilation as part of their care. Administration of analgesia and sedation to ensure patient comfort and facilitate mechanical ventilation must be balanced against the known negative consequences of excessive sedation. The present review focuses on the current evidence for sedation management during mechanical ventilation, including choice of sedatives, sedation strategies, and special considerations for acute respiratory distress syndrome (ARDS).

Recent findings—The Society of Critical Care Medicine recently published their updated clinical practice guidelines for analgesia, agitation, sedation, delirium, immobility, and sleep in adult patients in the ICU. Deep sedation, especially early in the course of mechanical ventilation, is associated with prolonged time to liberation from mechanical ventilation, longer ICU stays, longer hospital stays, and increased mortality. Dexmedetomidine may prevent ICU delirium when administered nocturnally at low doses; however, it was not shown to improve mortality when used as the primary sedative early in the course of mechanical ventilation, though the majority of patients in the informing study failed to achieve the prescribed light level of sedation. In a follow up to the ACURASYS trial, deep sedation with neuromuscular blockade did not result in improved mortality compared to light sedation in patients with severe ARDS.

Summary—Light sedation should be targeted early in the course of mechanical ventilation utilizing daily interruptions of sedation and/or nursing protocol-based algorithms, even in severe ARDS.

Keywords

acute respiratory distress syndrome; mechanical ventilation; sedation

INTRODUCTION

Respiratory failure requiring mechanical ventilation is a frequent complication of critical illness. Appropriate administration of analgesia and sedation is an essential component of the care of mechanically ventilated patients and requires knowledge of the available therapeutic agents and strategies for sedation. The goal of sedation for the mechanically

Correspondence to Bhakti K. Patel, MD, 5841 S. Maryland Avenue, Chicago, IL 60637, USA. Tel: +1 773 702 1000; fax: +1 773 702 4736; bpatel@medicine.bsd.uchicago.edu.

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ventilated patient in the ICU is to ensure patient comfort and safety while facilitating patient–ventilator interactions. Sedation practices in the ICU have shifted drastically over the past 30 years as a mounting body of evidence emerged supporting the use of lighter sedation with daily interruption and nursing-driven scale-based protocols over the previously ubiquitous deep sedation strategies. The Society of Critical Care Medicine (SCCM)'s Clinical Practice Guidelines for the Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) were recently published in 2018 and provide updated expert guidelines. Despite the growing body of literature, there are still many challenges with sedation management for a specific population of mechanically ventilated patients, those with acute respiratory distress syndrome (ARDS).

ANALGESIA

All sedation strategies should start with assessing for and ensuring adequate pain control. Pain is a frequently experienced and distressing symptom of critical illness and can result from mechanical ventilation itself, invasive procedures and monitoring devices, or other aspects of routine care in the ICU [1]. The 2018 PADIS guidelines recommend adequately treating pain before considering administration of sedation [2■■]. Direct patient communication should be used whenever possible to assess pain, though this may be difficult in mechanically ventilated patients. Several validated tools are available to assist with pain assessment in critically ill patients including the Numeric Rating Scale, Visual Analog Scale, and Behavioral Pain Scale [3]. In patients who are unable to communicate directly, the Nonverbal Pain Scale can be used and has been shown to correlate with painful stimuli [4].

The opioid class of medications is the mainstay for pain relief during mechanical ventilation, as they are potent analgesics and facilitate ventilator synchrony by depressing respiratory drive. The most commonly used opioids in the ICU include morphine, hydromorphone, fentanyl, and remifentanil. The intravenous route is the preferred route of administration in critically ill patients given faster onset of action and ease of dose titration. Opiates are hepatically metabolized and the metabolites are renally cleared. Morphine has active metabolites that can accumulate in patients with renal dysfunction and should be avoided in such patients, while hydromorphone is metabolized to an inactive metabolite. Fentanyl is highly lipophilic, resulting in a rapid intravenous onset of action and potential for accumulation in fatty tissues after prolonged infusions or repeated dosing [5]. Remifentanil is a newer opiate that is metabolized by nonspecific enzymes independent of liver and kidney function to inactive metabolites. Its use has been associated with reduction in duration of mechanical ventilation and ICU length of stay when compared to other opiates [6,7].

SEDATION

Administration of sedation should only be considered after achieving adequate analgesia. Some patients may require no sedation with proper pain control [8], though frequently sedatives are needed to ensure patient comfort, safety, and synchrony with mechanical

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ventilation. When sedation is required, close attention should be paid to both the choice of sedative and the chosen strategy for administration.

SEDATIVE MEDICATIONS

An overview of randomized clinical trials comparing sedatives in mechanically ventilated patients in a medical and mixed population ICU can be found in Table 1 [9–19]. The most frequently used sedatives in the ICU are benzodiazepines, propofol, and dexmedetomidine. Benzodiazepines are potent anxiolytics, hypnotics, and sedatives and can also induce anterograde amnesia. Both midazolam and lorazepam are hepatically metabolized resulting in an increased duration of action in patients with liver dysfunction [3]. Though midazolam is shorter acting than lorazepam, it has renally cleared active metabolites which can accumulate in the setting of renal dysfunction and should be avoided in such patients [20]. Although benzodiazepines were traditionally used as first line agents for sedation, their use in the ICU is highly associated with the development of delirium [21], and randomized controlled trials have shown worse outcomes including oversedation and prolonged mechanical ventilation when compared with alternative agents such as propofol and dexmedetomidine [11,14–18,22,23].

Propofol is a sedative and hypnotic agent that can induce amnesia similar to benzodiazepines but offers a faster onset and offset of action allowing far more rapid titration. Although generally considered well tolerated, hypotension because of systemic vasodilation is a common side effect, and hypertriglyceridemia must be monitored for given its lipid emulsion formulation [5]. The propofol-related infusion syndrome is an uncommon and life-threatening adverse effect characterized by bradycardia, cardiac failure, rhabdomyolysis, severe metabolic acidosis, and acute renal failure with a mortality that ranges widely in the literature from 20 to 80% [24]. Clinical trials comparing propofol with benzodiazepines in critically ill mechanically ventilated patients have consistently shown propofol results in faster wake up times and fewer days on mechanical ventilation [11,14–16]. Fospropofol is a water-soluble prodrug of propofol that avoids the problems associated with a lipid emulsion formulation and is emerging as a viable alternative to propofol. Limited data suggest that it is well tolerated and effective when used as a sedative for mechanically ventilated adults, but further study is needed before widespread adoption in the ICU [25].

Dexmedetomidine is a centrally acting selective α_2 adrenergic receptor agonist with both analgesic and sedative effects, and, unlike other sedatives, does not depress the respiratory drive [26]. While originally approved by the U.S. Food and Drug Administration for short-term use, multiple clinical trials have subsequently demonstrated its efficacy and safety when used for longer term sedation in the ICU [17,18,22,23]. The main side effects of dexmedetomidine are bradycardia, hypotension and the potential for withdrawal symptoms upon discontinuation of long-term therapy [17,18]. When compared to other sedatives, dexmedetomidine has been shown to result in a more awake and interactive patient, a lower incidence of delirium, more ventilator free days, and less days in the ICU [17–19,22,23,27,28]. In addition, a recent double-blinded, randomized, placebo-controlled clinical conducted by Skrobik *et al.* [29■■] found a reduction in the incidence of delirium

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with low-dose nocturnal dexmedetomidine. For these reasons, the 2018 PADIS guidelines recommend either propofol or dexmedetomidine for sedation over benzodiazepines [2■■].

Given the previously demonstrated benefits of dexmedetomidine, and suggestions of a mortality benefit in certain populations [27,30], Shehabi *et al.* [31■■] recently published the results of a large, multicenter, randomized controlled trial studying early dexmedetomidine in mechanically ventilated patients. The study showed no difference in mortality at 90 or 180 days, or in ventilator free days. However, more than half the patients in both groups failed to achieve the targeted light sedation goal and three quarters of patients in the dexmedetomidine group also received propofol, benzodiazepines, or both. Interestingly, there was heterogeneity with respect to mortality when comparing patients above and below the median age of 63.7 years, with older patients showing a lower mortality and younger patients a higher. The authors postulated these findings may be because of age-related pharmacokinetic changes. Although another postulation is the age related benefit of the delirium protective effects of dexmedetomidine, as delirium is a known independent predictor of mortality among mechanically ventilated patients in the ICU [32]. Further study is needed to confirm these findings.

Volatile anesthetic agents, such as isoflurane and sevoflurane, have been used in the operating room for decades, but have not yet established a role in the sedation of mechanically ventilated patients in a general ICU setting. Their bronchodilatory and cardioprotective properties, rapid onset and offset of action, and lack of dependence on renal and hepatic function offer an attractive and novel option for ICU sedation, but their use has been mostly limited by the technical challenges of scavenging systems, limited familiarity among intensivists, and lack of robust clinical data on their use in this setting [33]. Recently, devices have become available that allow the use of volatiles with mechanical ventilators, avoiding the need for large anesthesia machines [34]. Outside of the operative and postoperative setting, several trials have demonstrated that these agents are well tolerated, efficacious, and allow for quicker wake up times and earlier extubation compared to traditional sedative agents [34–37].

SEDATION STRATEGIES

Whenever sedation is administered in the ICU, a strategy to ensure the appropriate level of sedation is reached while avoiding over sedation should be used. Available strategies include no sedation, daily interruption of sedation, and nursing directed algorithms utilizing validated scales such as the Richmond Agitation-Sedation Scale [38]. Continuous use of intravenous sedation is associated with prolonged mechanical ventilation [39]. In a landmark study by Kress *et al.* [40], a daily interruption of sedative infusions was shown to reduce the length of mechanical ventilation and ICU stay, and allowing for improved neurologic assessment resulting in fewer diagnostic neurologic testing. Follow up study showed that daily interruption of sedation also reduced the rate of common complications of critical illness such as ventilator associated pneumonia, venous thromboembolism, and bacteremia [41]. Pairing the daily interruption of sedation with a spontaneous breathing trial was also shown to result in improved patient outcomes [42]. Nursing-driven protocols targeting a specific sedation level have also been shown to be effective strategies for reducing both days

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on mechanical ventilation and in the ICU [43,44]. The best strategy for sedation however may be using no sedation at all. Strom *et al.* [8] not only showed that a 'no sedation' strategy with morphine alone was feasible, but that is also resulted in fewer days of mechanical ventilation, less time in the ICU, and shorter hospital stays. Despite concern of worse psychological outcomes with strategies focusing on minimizing sedation, long-term follow up of patients who received daily interruptions of sedation and a no sedation strategy did not show worse psychological outcomes, and in fact suggested lower rates of posttraumatic stress disorder with a daily interruption of sedation [45–47].

Multiple studies since have looked at both the short-term and long-term effects of sedation level, particularly early in the course of mechanical ventilation. In a multicenter, prospective longitudinal cohort study, Shehabi *et al.* [48] found that deep early sedation, defined as within the first 48 h of mechanical ventilation, was independently associated with longer mechanical ventilation, increased in hospital mortality, and higher 6-month mortality. Another multicenter prospective cohort study by Tanaka *et al.* [49] again showed deep sedation within the first 48 h increased the time to liberation and ICU and in hospital mortality independent of severity of illness. Follow up study continued to corroborate these findings, and showed a dose-dependent relationship between sedation intensity and mortality, length of mechanical ventilation, and delirium [50▪,51]. Based on these and other similar studies, the 2018 PADIS guidelines recommend a light level of sedation over heavy sedation for mechanically ventilated adult patients along with either daily interruptions of sedation or nursing protocolized targeted sedation [2▪▪]. Despite these recommendations, early deep sedation remains commonplace, and strategies for minimizing sedation such as spontaneous awakening trials have been slow to be incorporated into clinical practice [52,53▪▪].

SEDATION IN ACUTE RESPIRATORY DISTRESS SYNDROME

Though many of the key clinical trials examining sedation in the ICU included patients with ARDS, few provide data on optimal sedation targets specific to this unique patient population. Several management aspects of ARDS can make light sedation strategies challenging, including low tidal volume ventilation, high positive end expiratory pressure (PEEP), paralysis, and prone positioning. Although historically deep sedation was thought to be required to allow patients to tolerate lung protective ventilation with low tidal volumes and high PEEP, studies have shown that these strategies in fact do not require increased sedation use [54,55]. Neuromuscular blockade has been used on occasion for severe ARDS, necessitating the use of deep sedation, based on the results of a multicenter randomized controlled trial conducted in France demonstrating a mortality reduction when neuromuscular blockade was used early for 48 h [56]. This study was double blinded, however, and prescribed deep sedation, a therapy now known to result in worse outcomes, to both the intervention and control arm. The Prevention and Early Treatment of Acute Lung Injury investigators recently published the results of a large, multicenter trial conducted in the United States, which compared early neuromuscular blockade with a strategy of light sedation, consistent with the current PADIS guidelines, with a primary endpoint of 90-day mortality [57]. The study was stopped early for futility after enrollment of 1006 patients, showed no difference in mortality, and demonstrated a higher rate of adverse cardiovascular

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events and more immobility in the group receiving neuromuscular blockade paired with deep sedation, further supporting the use of light sedation goals for patients with ARDS.

Balanced against the light sedation target is the goal of preventing self-induced lung injury from spontaneous respirations and other ventilator asynchronies [58,59]. Although breath stacking is frequently dealt with by increasing the level of sedation, adjusting the ventilator has been shown to be a more effective method for reducing patient–ventilator asynchrony [60]. Animal models have suggested that strong spontaneous efforts during mechanical ventilation may perpetuate lung injury [61], although in models with less severe injury spontaneous efforts were found to be beneficial to lung recruitment [62]. Eliminating spontaneous respirations, however, with either deep sedation or neuromuscular blockade results in marked diaphragm atrophy in as little as 18 h of diaphragm inactivity [63]. Ensuring optimal lung recruitment may mitigate the injurious effects of spontaneous breathing while allowing for the benefits, such as minimization of diaphragm atrophy and sedation administration. Novel approaches to ARDS management such as noninvasive ventilation delivered by helmet may allow for optimal lung recruitment prior intubation, obviating the need for mechanical ventilation and sedation at all [64].

CONCLUSION

Appropriate analgesia and sedation are critical aspects of the management of mechanically ventilated patients in the ICU. After adequate analgesia is ensured, a nonbenzodiazepine sedative such as dexmedetomidine or propofol should be used if sedation is needed, though analgesia alone may be adequate. When sedation is administered, a light level of sedation should be targeted utilizing daily interruptions of sedation or nursing protocols with validated sedations scales. Avoiding benzodiazepines and deep sedation results in less delirium, shorter duration of mechanical ventilation, and improved mortality. As light sedation inevitably results in increased spontaneous respiratory effort, further study is needed to determine the tradeoffs between deeper sedation and spontaneous respiration, particularly in severe ARDS.

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KEY POINTS

- Adequate analgesia should be ensured with a validated pain assessment tool before administering sedation.
- When choosing a sedative, benzodiazepines should be avoided in favor of dexmedetomidine or propofol.
- Daily interruptions of sedation, nursing protocol-based algorithms, or both should be used to minimize sedation.
- Appropriate use of sedatives in mechanically ventilated patients results in less delirium, shorter duration of mechanical ventilation, decreased ICU and hospital length of stay, and a reduction in mortality.

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Table 1.

Overview of randomized controlled clinical trials comparing sedative agents

Study	Year	Medications	Patients	Results
Pohlman *et al.* [9]	1994	Lorazepam vs. midazolam	20 medical ICU patients	Trend to faster wake up with lorazepam
Swart *et al.* [10]	1999	Lorazepam vs. midazolam	64 medical ICU patients	Less expensive and more effective sedation with lorazepam
Kress *et al.* [11]	1996	Propofol vs. midazolam	73 medical ICU patients	Faster wake up and equally effective sedation with propofol
Chamorro *et al.* [12]	1996	Propofol vs. midazolam	98 medical ICU patients	Faster wake up and more effective sedation with propofol
Barrientos-Vega *et al.* [13]	1997	Propofol vs. midazolam	108 medical/surgical ICU patients	Equally effective and more cost-effective sedation, fewer days on mechanical ventilation with propofol
Weinbroum *et al.* [14]	1997	Propofol vs. midazolam	67 ICU patients	Equally effective sedation, midazolam more cost effective
Hall *et al.* [15]	2001	Propofol vs. midazolam	99 medical/surgical ICU patients	Fewer days on mechanical ventilation with propofol
Carson *et al.* [16]	2006	Propofol vs. midazolam	132 medical ICU patients	Fewer days on mechanical ventilation with propofol
Pandharipande *et al.* [17]	2007	Dexmedetomidine vs. lorazepam	106 medical/surgical ICU patients	Less delirium and coma and more on target sedation with dexmedetomidine
Riker *et al.* [18]	2009	Dexmedetomidine vs. midazolam	375 medical/surgical ICU patients	Less delirium and fewer days on mechanical ventilation with dexmedetomidine
Dasta *et al.* [19]	2010	Dexmedetomidine vs. midazolam	366 medical/surgical ICU patients	Lower total ICU costs with dexmedetomidine

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