Optimizing Sustained Use of Sedation in Mechanically Ventilated Patients: Focus on Safety

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Abstract: Optimizing sustained use of ICU sedation in mechanically ventilated patients requires careful consideration of drug-specific characteristics (E.G. pharmacokinetics), consideration of potential adverse effects in susceptible patients, and utilization of sedation-minimizing strategies. In the era of anxiolytic dosing protocols adjusted to specific patient behaviors as defined by sedation scales in conjunction with daily interruption, midazolam is a reasonable option for long-term sedation. Propofol is an appealing agent for ICU sedation due to it’s pharmacokinetic profile and a reduced propensity to result in prolonged sedation. However, care should be taken to monitor for potential devastating adverse effects including hypertriglyceridemia and propofol-related infusion syndrome (PRIS). Dexmedetomidine unreliably provides adequate sedation at doses currently approved by the FDA, though upward titration of dexmedetomidine coupled with rescue benzodiazepines and/or fentanyl appears to be safe and comparable to benzodiazepines in the achievement of light to moderate Richmond Agitation Sedation Scale (RASS) goals. Clinicians should closely monitor patients receiving dexmedetomidine for hemodynamic-altering bradycardia. Strategies that promote frequent patient assessment with corresponding sedative dose minimization have demonstrated the benefits of limiting oversedation. Implementation of a sedation protocol requires careful consideration of ICU resources and staffing such that efforts made are sustainable and will be safe and effective for the patient population affected.

Keywords: Sedation, propofol, midazolam, lorazepam, dexmedetomidine, delirium, patient safety.

INTRODUCTION

The administration of pharmacologic agents for anxiolysis and analgesia in mechanically ventilated patients, collectively referred to as intensive care unit (ICU) sedation, should be a focus of patient safety from both the therapeutic and toxicity perspective. The therapeutic intent of sedation is to provide comfort and aid in prevention of patient injury that could be induced by positive pressure ventilation (i.e. volutrauma and barotrauma) or by overt injury such as premature self-extubation and catheter removal necessary for the care of the critically ill patient. At the same time, avoiding toxicity, namely prolonged durations of mechanical ventilation and delirium, as well as minimizing adverse effects common to each anxiolytic and analgesic agent should be emphasized. The goal of this paper is to provide an update of the ICU sedation literature focusing on benzodiazepines, propofol, dexmedetomidine, and sedation-minimizing strategies.

BENZODIAZEPINES

Benzodiazepines including diazepam, lorazepam, and midazolam are the agents most commonly administered to provide anxiolysis in the ICU setting dating back to 1990 and continuing in current practice as recommended by the 2002 Society of Critical Care Medicine (SCCM)/American Society of Health-Systems Pharmacists (ASHP) guidelines for sedatives and analgesics [1-4].

Several pharmacokinetic differences exist amongst the most commonly used benzodiazepines administered for ICU sedation and knowledge of these properties will optimize patient care and patient safety. Diazepam has a relatively rapid onset of action, making it an appropriate option for initiation or induction of sedation in an acutely agitated patient. However, due to its long half-life and the presence of active metabolites (desmethyl-diazepam, nordiazepam), prolonged use of diazepam can potentially result in delayed awakening, difficulty in weaning from the ventilator, and ultimately a longer length of stay (LOS) [4]. Lorazepam has a slower onset of action and therefore is not ideal for treating acutely agitated patients. Both intermittent or continuous IV administration are recommended for long-term sedation; however, if a continuous infusion is selected, rapid titrations in dose should be avoided as they are likely to be of limited clinical benefit given this agent’s intermediate half-life. It is important to note that the solvents used for lorazepam, polyethylene glycol (PEG) and propylene glycol (PG), have been associated with acute tubular necrosis of the kidney, lactic acidosis and hyperosmolar states [4]. With prolonged administration and/or escalating lorazepam doses, patients are at risk for developing these adverse effects and serial monitoring of the osmol gap should ensue with consideration of drug discontinuation if a value of 10 or greater is calculated [5, 6]. Midazolam is frequently the agent of choice to manage acutely agitated patients with bolus injections as it demonstrates a very rapid onset of action (2 to 5 minutes). Additionally, midazolam may be used as a continuous infusion for ongoing sedation and in contrast to lorazepam, more frequent dose adjustments can be made in response to acute agitation due to its shorter half-life. One disadvantage of midazolam is the presence of an active metabolite (alpha-hydroxymidazolam), that can accumulate, especially in renal failure, and can contribute to prolonged or excessive sedation. For this reason, the SCCM / ASHP guidelines only recommend this agent for management of acute agitation if sedation is planned to be less than 48 hours [4]. However in the era of sedation protocols targeted to sedation scale goals and daily sedative interruption, this recommendation may be outdated as described later.

There are a limited number of studies comparing individual benzodiazepine agents for continuous sedation in critically ill patients (Table 1). In brief, comparisons of lorazepam and midazolam for long-term sedation have demonstrated that targeted levels of sedation could be achieved easily with either agent [7-10], and no differences in measures of hemodynamic indices (e.g. cardiac index, mean arterial pressure, pulmonary artery occlusion pressure) or oxygen transport (e.g. arterial oxygen or oxygen consumption) were observed between the two agents [8]. Midazolam appeared to be a less potent sedative as reflected by the higher doses of this agent that were required compared to lorazepam for the duration of the study period [7-10]. One trial
discussed that the pharmacokinetic differences between agents translates into observed differences in clinical outcomes including prolonged sedation with lorazepam and ease of titration with midazolam [10]; however these were not observed in the other trials [7-9].

There are several important characteristics of these trials that should be noted. As seen in Table 1, most of the trials had relatively small sample sizes and were performed at single centers. Except for one trial, all investigations were open-label which could introduce investigator bias. Additionally, the trials did not describe whether they stratified patients for severity of illness or prior use of sedative agents. Most of the trials studied medical or surgical patients, making extrapolation to other patient populations (cardiac, neurology / neurosurgery) difficult. Lastly, each trial used unique sedation scales, specific to each study as opposed to a more descriptive, contemporary tool such as the Sedation-Agitation Scale (SAS) [11] or the Richmond Agitation-Sedation Scale (RASS) commonly utilized today [12, 13]. As a result, the methodology of these trials may or may not translate into today’s practice where lighter levels of sedation are targeted and as a result lower doses of benzodiazepines are administered.

PROPOFOL

Propofol is an intravenous anesthetic agent approved by the FDA in 1993 for sedation in the mechanically-ventilated ICU population and has since been widely used due to its rapid onset and offset. Propofol is a highly lipophilic agent that demonstrates 3 compartment model pharmacokinetics; the first compartment representing plasma, the second rapidly equilibrating tissues, and the third slowly equilibrating tissues. The distribution phases into these 3 discrete compartments are associated with a half-life of 2-8 minutes, 30-70 minutes, and 4-24 hours, respectively. Despite the long terminal half-life, recovery from the clinical effects of propofol is rapid, but is proportional to the rate and duration of the infusion. Combined, the pharmacokinetic parameters of propofol afford prompt central nervous system penetration followed by rapid elimination from plasma, neither of which is significantly altered by renal or hepatic impairment [14].

The efficacy of long-term propofol use has been extensively evaluated in the critically ill, high-risk, and elderly patient populations, but the infusion is not without significant risks [15]. The lipid formulation provides an environment conducive to microbial growth and contains egg lecithin which can cause severe reactions in allergic patients. In effort to minimize the risk of infection, the package labeling for propofol recommends replacing intravenous tubing every 12 hours [14]. The emulsion may also induce hypertriglyceridemia which generally has been documented to occur after 3 days of initiation and can precipitate acute pancreatitis [16]. The SCCM/ASHP guidelines recommended monitoring triglyceride concentrations after 2 days of continuous infusion and routinely thereafter until propofol is discontinued [4]. If a triglyceride concentration of 400 mg/dl or more is measured, serious consideration should be given to discontinuing propofol. From a nutrition standpoint, the lipid formulation supplies 1.1 kcal/ml which should be taken into consideration when determining a patient’s total daily caloric intake. Independent of the effects associated with the lipid-based solvent, propofol infusion commonly induces hemodynamic instability including hypotension, moderate bradycardia, and decreased cardiac output, all of which are more likely to occur as the dose escalates and when administered concomitantly with opiates [14]. Of greatest consequence from a toxicity perspective is the potential for increased patient morbidity and mortality associated with propofol-related infusion syndrome (PRIS). PRIS encompasses a constellation of clinical features including metabolic acidosis, rhabdomyolysis, acute renal failure, hepatomegaly, hyperkalemia, lipemia, and cardiovascular collapse. Arrhythmias including atrial fibrillation, bradycardia, bundle branch block, ventricular tachycardia and asystole have also been reported (Table 2) [17]. The incidence of PRIS is unknown as no formal registry exists to record patients who develop the syndrome, but since the first case reports in 1992, more than 35 children and approximately 40 adults have demonstrated signs and symptoms suggestive of PRIS [18-25]. Following discontinuation of the propofol infusion, treatment of the syndrome is primarily supportive and the associated mortality is high. A recently published retrospective database analysis evaluated 1,139 patients with suspected PRIS defined as at least 1 manifestation of the syndrome. Death occurred in 342 patients (30%), but interestingly, mortality was more likely if patients were ≤ 18 years of age (OR 2.3 [95% CI 1.7-3.2]) [26]. This finding is similar to those of a 2008 analysis that described all 33 pediatric case reports available at the time of publishing. The evaluation revealed a mortality rate of 64%; all patients were ≤ 16 years of age [25]. Therefore, with staggering mortality rates seen in both the adult and pediatric patient populations, prevention of the syndrome is paramount. PRIS prevention, however, is challenging as the mechanism by which the syndrome develops is poorly understood. Contemporary research has focused on mitochondrial respiratory chain dysfunction [27], but elevated levels of nonesterified fatty acids may also play a role in PRIS development [28]. Limited clinical risk factors have been identified which may distinguish patients at high risk for syndrome occurrence and include sepsis, significant cerebral injury, impaired oxygen delivery and receipt of high-dose propofol [29]. Doses greater than 67 mcg/kg/minute for at least 48 hours in children [30] and greater than 83 mcg/kg/minute in adults [31] appear to significantly increase the likelihood of PRIS development. Furthermore, the FDA has advised alternative sedation strategies be considered should patients require prolonged propofol infusions or increasing doses to maintain sedation, or if metabolic acidosis is detected after the initiation of the infusion, in an effort to prevent syndrome development [14].

Since the SCCM/ASHP guidelines were published, two important randomized controlled trials have been completed comparing propofol to other sedative agents. The first is an evaluation of dexmedetomidine vs midazolam or propofol which is discussed in detail below. The second is a trial of 132 medical intensive care unit patients randomized to intermittent lorazepam bolus administration (n=64) or continuous propofol infusion (n=68) [32]. Sedation in both groups was titrated to maintain a Ramsay score of 2 to 3 and interrupted on a daily basis. The duration of mechanical ventilation was the primary outcome and was significantly shorter in the propofol group as compared to the lorazepam group (5.8 vs 8.4 days; p<0.04); differences in ICU LOS (8.3 vs 10.4) and hospital LOS (18 vs 20) favored the propofol group, but did not reach statistical significance. Both agents were fairly well tolerated with 3 patients failing propofol therapy (1 each due to hypotension, bradycardia, and hypertriglyceridemia) and 5 patients failing lorazepam therapy due to inadequate sedation.

DEXMEDETOMIDINE

Dexmedetomidine is a unique sedative which provides anxiolytic activity via stimulation of presynaptic alpha2-adrenoreceptors at the level of the locus ceruleus within the central nervous system. With a mechanism of action similar to clonidine, typical adverse effects seen with this agent include hypotension, bradycardia and sinus arrest. In addition to its sedative properties, dexmedetomidine is also theorized to provide analgesia without the consequence of respiratory depression [33]. As a result, this sedative is an appealing option for the facilitation of mechanical ventilation.

Currently, the Food and Drug Administration recommends dexmedetomidine be administered as a loading dose of 1 mcg/kg administered over 10 minutes followed by a continuous infusion in doses not exceeding 0.7 mcg/kg/hour for a total duration of up 24 hours for the maintenance of ICU sedation [33]. Loading doses have typically been avoided in the clinical setting due to either
The first trial (MENDS) compared dexmedetomidine (n = 52) and lorazepam (n = 51), both titrated to a RASS goal dictated by the patient’s medical team and assessed twice daily [35]. The study portion of the sedative infusion was for a duration not to exceed 120 hours, at which time patients were switched to local sedation practices. During the 5-day study evaluation, the median (interquartile range) dose of dexmedetomidine was 0.74 mcg/kg/hour (0.39-1.04). Dexmedetomidine patients were observed to be within 1 point of the nurse-targeted RASS goal 80% of the time compared to 67% of the time for lorazepam-sedated patients (p = 0.04). The difference may have been a consequence of significant oversedation in the lorazepam group as indicated by deeper sedation than the nurse RASS score goal (33% v. 15%, p = 0.01) and the median number of days oversedated (2 days v. 1 day, p = 0.01) compared to dexmedetomidine. Patients randomized to dexmedetomidine appeared to have more frequent periods of undersedation due to pain (or possibly anxiety) as demonstrated by a higher median daily fentanyl requirement (575 mcg/day v. 150 mcg/day, p = 0.006) which was protocolized to be given as intermittent injections for acute pain or continuous infusion when maximum study sedative doses had been reached. As expected, patients in the dexmedetomidine group experienced a higher incidence of sinus bradycardia defined as a heart rate less than 60 beats per minute (17% v. 4%, p = 0.003) when compared to the lorazepam group. There was no difference in the occurrence of heart rate less than 40 in the 2 groups. All other hemodynamic variables including blood pressure and new arrhythmia as well as

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**Table 1. Prospective Trials Comparing Lorazepam and Midazolam for Continuous Sedation**

<table>
<thead>
<tr>
<th>Trial Reference</th>
<th>Trial Design</th>
<th>N</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Results</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Randomized, open-label, single center</td>
<td>Loraz = 10 Midaz = 10</td>
<td>Mechanically ventilated patients requiring benzodiazepines for sedation Age &lt; 18 yrs, pregnancy, primary CNS disease</td>
<td>Time to adequate sedation Max infusion rate Mean infusion rate Total drug administered Total time of infusion</td>
<td>124 mins 0.1 mg/kg/hr 0.06 mg/kg/hr 5.4 mg/kg 62 hrs</td>
<td>NS</td>
</tr>
<tr>
<td>8</td>
<td>Randomized, open-label, multicenter</td>
<td>Loraz = 50 Midaz = 45</td>
<td>Hemodynamically stable adult patients requiring sedation Pulmonary artery catheter placed in all patients Study only evaluated patient response to 8 hours of sedation Age &lt; 18 yrs, pregnancy, primary cardiac or neurosurgical disorder, hemodynamic instability, serious head injury, coma, receipt of NMB agents, disorder of lipid metabolism or acute narrow angle glaucoma</td>
<td>Hemodynamic profile: HR, MAP, CVP, CO, PAOP, mPAP, SVI, SVRI, PVRI, Oxygen transport variables: SaO2, MvO2, arterial O2 content, O2 delivery, O2 consumption, pulmonary shunt Quality of sedation: Patient Comfort Score, Nursing Score</td>
<td>No statistical difference in any of the HD or oxygen transport variables. Over the 8 hr study period, 2 readings of pulmonary shunt percentage were statistically different but were probably statistical anomalies. Patient Comfort Score and Nursing Sedation Score were similar between groups</td>
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</table>

Loraz=lorazepam; Midaz=midazolam; CNS=central nervous system; NS=not significant; NMB=neuromuscular blocking; HR=heart rate; MAP=mean arterial pressure; CVP=central venous pressure; CO=cardiac output; PAOP=pulmonary artery occlusion pressure; mPAP=mean pulmonary artery pressure; SVI=stroke volume index; SVRI=systemic vascular resistance index; PVRI=pulmonary vascular resistance index; SaO2=arterial oxygen saturation; MvO2=mixed venous oxygen saturation; O2=oxygen; HD=hemodynamic; ICU=intensive care unit; NR=not reported.

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hypotension induced by central alpha2a-mediated vasodilation or conversely hypertension triggered by vasoconstriction induced by peripheral alpha2b stimulation [34]. Additionally, outside of the cardiothoracic patient population where rapid extubation is often expected and observed, the 24-hour infusion indication severely limits dexmedetomidine use in patients requiring mechanical ventilation for acute respiratory failure. It is within this latter population of patients where several questions regarding the safe use of dexmedetomidine exist including: 1) does dexmedetomidine provide an adequate level of sedation at the doses recommended? and 2) are prolonged infusions associated with intensified or undiscovered adverse effects? Three recently published, randomized, double-blind, multi-centered trials help shed light on these issues.
other endpoints were similar between dexmedetomidine and lorazepam.

The second trial was a pilot study that evaluated the non-inferiority of dexmedetomidine (n = 38) versus either midazolam or propofol (n = 41), in maintaining a target RASS goal of either 0 to -3 or a deeper sedation goal of -4 [36]. The infusion of sedatives was allowed up to 14 days in an evenly split medical-surgical population. In the per-protocol analysis, dexmedetomidine patients [median (range): dose 0.8 (0.3-1.4) mcg/kg/hour; duration 40 (3-198) hours] met the target RASS of 0 to -3 a similar percentage of time when compared to midazolam or propofol (74% v. 64%, p > 0.05). However, when deeper levels of sedation were targeted (RASS -4), dexmedetomidine was inferior to the comparative group (42% v. 62%, p = 0.006). Combining targeted RASS goals, non-inferiority of dexmedetomidine compared to midazolam or propofol was not confirmed as indicated by crossing of the lower boundary of the confidence interval (prespecified as 0.90) for the estimated ratio between the 2 groups in time at target sedation [0.97 (95% confidence interval 0.79-1.15)]. Administration of fentanyl, other rescue sedation/analgesia, and the occurrence of serious adverse events including bradycardia were similar between groups.

Table 2. Clinical Features Most Commonly Reported with Propofol-Related Infusion Syndrome (PRIS)

<table>
<thead>
<tr>
<th>Acute Renal Failure</th>
<th>Atrial Fibrillation</th>
<th>Bradycardia</th>
<th>Cardiac Arrest</th>
<th>Fever</th>
<th>Hepatomegaly</th>
<th>Hyperkalemia</th>
<th>Hypotension</th>
<th>Lipemia</th>
<th>Metabolic Acidosis</th>
<th>Rhabdomyolysis</th>
</tr>
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</table>

A third study (SEDCOM) compared dexmedetomidine (n = 244) to midazolam (n=122) with the primary endpoint being the percentage of time within a RASS target of +1 to -2 [37]. Mean dexmedetomidine maintenance doses administered in the study were broken into 3 representative groups: 0.2-0.7 mcg/kg/hour in 39% of patients, 0.71-1.1 mcg/kg/hour in 32% or patients, and 1.11-1.4 mcg/kg/hour in 29% of patients over a median (IQR) duration of 3.5 (2.0-5.2) days. The percentage of time dexmedetomidine patients were within the target RASS range was similar to midazolam-sedated patients (77.3% v. 75.1%, p = 0.18). A significantly greater number of dexmedetomidine patients required open-label rescue midazolam (63% v. 49%, p = 0.02), indicating significantly more undersedation. Despite this, the percentage of patients requiring fentanyl and the median total dose of fentanyl were not different between groups. Oversedation as indicated by the need to interrupt study drug to maintain a RASS score of -2 to +1, was similar between dexmedetomidine and midazolam-sedated patients (91% v. 91.8%, p = 0.85). Interestingly, patients in the dexmedetomidine group had a significantly reduced median time to extubation compared to midazolam (3.7 days v. 5.6 days, p = 0.01) despite the similar overall level of sedation induced. This finding may be limited by the fact that over 36 hours elapsed from the time of ICU admission to the start of study drug in each group, with sedation administered in this interval in the majority of patients, the amount and depth of sedation of which were not reported. A significantly greater percentage of dexmedetomidine patients experienced bradycardia defined as a heart rate less than 40 or a 30% decrease from pre-study baseline measurements (42.2% v. 18.9%, p < 0.001).

Additionally, 12 out of 103 patients with bradycardia in the dexmedetomidine group and 1 out of 22 patients in the midazolam group required rescue therapy with atropine or glycopyrrolate for profound bradycardia. Tachycardia, hypertension, and secondary infection were more commonly observed in the midazolam group and hyperglycemia more common in the dexmedetomidine-treated patients. Importantly, it was noted that rebound hypertension and tachycardia did not occur upon abrupt discontinuation of dexmedetomidine.

Delirium is a variable of interest in the intensive care unit patient as it has been associated with increases in sedative dose and duration, physical restraint use, length of stay and mortality [38-40]. As such, selecting an anxiolytic that decreases the frequency and/or duration of delirium would be potentially beneficial to aid in minimizing these consequences. Each of the aforementioned dexmedetomidine trials place emphasis on the recognition of delirium as defined by the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [41]. The median number of days alive without delirium or coma was the primary outcome of interest in the MENDS trial. Compared to lorazepam, dexmedetomidine significantly increased the composite of delirium-free and coma-free days over a 28-day period [median (IQR) 7 days (1,10) v. 3 days (1,6), p = 0.01] [35]. This finding should be interpreted with caution as the signal from the reported beneficial effect was derived from a reduction in coma-free and not delirium-free days. This corresponded with the significantly greater frequency of oversedation in the lorazepam group as described above. The SEDCOM trial found a reduction in the prevalence of delirium (54% v. 76.6%, p < 0.001) as well as an increase in the mean number of delirium-free days (2.5 days v. 1.7 days, p = 0.002) compared to midazolam [37]. Conversely, the pilot study found a significantly higher prevalence of delirium in the dexmedetomidine group compared to midazolam or propofol (43.9% v. 25%, p = 0.035) [36].

STRATEGIES TO MINIMIZE OVERSEDATION

Regardless of the sedative agent that is used potential exists for oversedation to occur, which may lead to adverse outcomes including increased duration of mechanical ventilation, incidence of nosocomial infection, and lengths of stay. This has been demonstrated particularly when continuous infusions of sedative agents are employed for ongoing sedation [42]. Fortunately, multiple studies have demonstrated that implementing strategies that promote frequent assessment of sedation needs as well as minimization of sedative dose can be effective in avoiding excessive sedation and its untoward consequences. The two most commonly cited methods are nursing-directed sedation protocols and daily interruptions of sedatives, both of which are recommended in the sedation guidelines. Another important consideration that should not be entirely separated from this discussion is the approach to weaning from the mechanical ventilator and the logistics of managing sedation in conjunction with these practice decisions. These strategies and the supporting literature will herein be reviewed and the reader is referred to Table 3 for study details.

The effects of a nursing-implemented sedation protocol whereby ICU nurses made frequent assessments of the level of sedation using the Ramsay sedation scale and according to a designed protocol then made adjustments in sedative dose to maintain the goal level of sedation was first published a decade ago [43]. As compared to the standard of care (sedative adjustment per physician order), this led to significant decreases in duration of mechanical ventilation and also ICU length of stay. Further support for this practice comes from a before-after study of a nursing-implemented sedation protocol that included over 400 medical ICU patients [44]. Relative to the standard care group, the protocol group had a significantly decreased incidence of ventilator-associated pneumonia in addition to the aforementioned benefits.
Pharmacists can also play an important role in development and adherence to sedation protocols and such involvement has been demonstrated to lead to similar reductions in duration of mechanical ventilation and ICU length of stay [45]. Some investigations of nursing-directed sedation protocols have failed to show these benefits, which underscore the importance of making institution and unit-specific considerations and also assessing the impact of practice changes that are implemented [46, 47]. One notable advantage of sedation protocols is that they can be implemented into routine care without excessive utilization of already available resources.

A second method to minimize oversedation that has been studied is a once-daily interruption of sedatives to allow time for drug clearance and re-evaluation of sedative needs. In a

![Table 3. Prospective Trials Comparing Nursing-Directed Sedation Protocols to Standard of Care](image-url)

Prospective trials comparing daily pharmacist intervention to enforce sedation guideline versus sedation according to guidelines without pharmacist intervention.

Prospective trials comparing daily interruption of sedatives versus standard care.

Prospective trials comparing Combined daily awakening and spontaneous breathing trial protocols versus Spontaneous breathing trial protocol only.

*Results are presented as mean +/- standard deviation or median (Interquartile range). Abbreviations used as follows: I=Intervention group, C=Control group. In all cases the order of results is presented as Intervention vs Control group.
prospective, randomized trial implementation of daily sedative interruption reduced the duration of mechanical ventilation, ICU LOS, and reducing oversedation. In addition to these benefits, fewer patients received diagnostic testing to assess mental status [48]. Concerns that have limited the application of this practice include this being a single-center study that involved care by investigators outside of routine care provided by available staff. Additionally, some remain apprehensive about the possibility for increased patient self-harm as a result of uncontrolled agitation that may arise while patients are off all sedatives.

A recent prospective, randomized trial of 335 patients (ABC Trial) from four centers also demonstrated significant benefits when implementing a daily interruption strategy in addition to a spontaneous breathing trial (SBT) protocol [49]. Specifically, sedative dose was reduced, patients were more alert as assessed by the Richmond Agitation Sedation Scale (RASS) at the time of first successful SBT, incidence of coma was reduced, days free from mechanical ventilation were increased, and ICU and hospital LOS were decreased. For the first time a significant reduction in 1-year mortality was also demonstrated. Self-extubations did occur more frequently in the daily interruption group, but did not result in a higher rate of reintubations. In this trial the interventions were carried out without the assistance of study investigators, providing further support for this intervention to be easily incorporated into practice.

In the ABC trial reviewed above, sedative interruption was performed in conjunction with a SBT protocol. This makes sense logistically and may help to optimize mental status at the time a decision is ready to be made regarding extubation. Although a thorough review of mechanical ventilation weaning practices is beyond the scope of this review it is important to recognize that protocols utilizing a standardized approach to mechanical ventilation weaning and assessment have demonstrated significant reductions in time on the ventilator in multiple investigations [50-52]. Therefore, mechanical ventilation weaning practices must be considered and included in the content of any sedation protocol.

**SUMMARY**

Optimizing sustained use of ICU sedation in mechanically ventilated patients requires careful consideration of drug-specific characteristics (e.g. pharmacokinetics), consideration of potential adverse effects in susceptible patients, and utilization of sedation-minimizing strategies. Currently, the SCCM / ASHP guidelines recommend the use of midazolam for induction of sedation in acutely agitated patients and the use of lorazepam for continuous sedation given the differences in pharmacokinetic profiles. However, in the era of sedation protocols and daily benzodiazepine interruption, this recommendation is likely outdated and midazolam is a reasonable option for long-term sedation. Propofol is an appealing agent for ICU sedation due to its pharmacokinetic profile and a reduced propensity to result in prolonged sedation. Despite this, care should be taken to monitor for potential devastating adverse effects including hypertriglyceridemia and PRIS. Based on the current literature, it is unlikely that dexmedetomidine reliably provides adequate sedation at doses currently approved by the FDA. Upward titration of dexmedetomidine coupled with rescue benzodiazepines and/or fentanyl appears to be comparable to benzodiazepines in the achievement of light to moderate RASS goals. It appears that prolonged infusions of dexmedetomidine are safe, with the noted caveat of an increased risk of bradycardia. Lastly, strategies that promote utilizing the minimal sedative dose required have demonstrated the benefits of limiting oversedation. When implementing a sedation protocol ICU, resources and staffing should be considered so as to implement a strategy that is sustainable and will be safe and effective for the patient population affected. The approach to weaning from mechanical ventilation must also be incorporated in the design of sedation protocols.

**REFERENCES**


