Daily Sedation Interruption Versus Targeted Light Sedation Strategies in ICU Patients

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Objective: The updated clinical practice guidelines for the management of pain, agitation, and delirium recommend either daily sedation interruption or maintaining light levels of sedation as methods to improve outcomes for patients who are sedated in the ICU. We review the evidence supporting both methods and discuss whether one method is preferable or if they should be used concurrently.

Data Source: Original research articles identified using the electronic PubMed database.

Study Selection and Data Extraction: Randomized controlled trials and large prospective cohort studies of mechanically ventilated ICU patients requiring sedation were selected.

Data Synthesis: The methods of daily sedation interruption and targeting light sedation levels (including avoidance of deep sedation) are safe in critically ill patients with no increase, and a potential decrease, in long-term psychiatric disturbances. Randomized trials comparing these methods with standard care, which has traditionally involved moderate to heavy sedation, found that both methods reduced duration of mechanical ventilation and ICU length of stay. Additionally, one trial noted that daily sedation interruption paired with spontaneous breathing trials improved 1-year survival, whereas a large observational study found that deep sedation was associated with decreased 180-day survival. Two common characteristics of these interventions in trials showing benefits were avoidance of deep levels of sedation and significant reductions in sedative doses, especially benzodiazepines. Thus, combining targeted light sedation with daily sedation interruption may be more beneficial than either method alone if sedative doses are reduced and arousal and mobility are facilitated during the ICU stay.

Conclusion: Daily sedation interruption and targeting light sedation levels are safe and proven to improve outcomes for sedated ICU patients when these approaches result in reduced sedative exposure and facilitate arousal. It remains unclear as to whether one approach is superior, and further studies are needed to evaluate which patients benefit most from either or both techniques. (Crit Care Med 2013; 41:S39–S45)

Key Words: arousal; interruption; outcomes; sedation

Agitation and anxiety occur commonly in critically ill patients. In addition to being unpleasant and often disturbing to patients, these symptoms can lead to increased endogenous catecholamine activity and oxygen consumption, hypermetabolism, and immunosuppression. Sedative medications are typically administered to critically ill patients in order to treat agitation, to improve synchrony with mechanical ventilation, and to decrease patients’ physiologic stress response. Administration of sedatives to critically ill patients may be complicated by unpredictable pharmacokinetics and pharmacodynamics due to impaired organ function, drug interactions, altered protein binding, and fluctuating volumes of distribution. ICU providers also often assume that deep sedation is psychologically beneficial to critically ill patients to reduce the patients’ chances of recalling unpleasant events during their ICU stay. As a result, ICU patients are often deeply sedated to the point that they may respond only to painful stimuli.

A growing body of research has shown that maintaining deep sedation in critically ill patients is associated with numerous adverse patient outcomes, including longer durations of mechanical ventilation, prolonged ICU stays, and increased brain dysfunction (delirium and coma) (1). Recently, Shehabi et al (2) examined the effects of deep sedation in a multicenter prospective

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cohort study of medical and surgical ICU patients. They assessed arousal level every 4 hours using the Richmond Agitation-Sedation Scale (RASS) (3) and classified scores between –3 and –5 as deep sedation. A greater number of assessments meeting the deep sedation criteria during the first 48 hours was independently associated with increased time to extubation (hazard ratio, 0.90; \(p < 0.001\)), with each additional occurrence of deep sedation increasing the time to extubation by over 12 hours. In addition, each additional occurrence of early deep sedation was independently associated with a 10% increased risk of in-hospital death (hazard ratio, 1.11; \(p = 0.01\)) and an 8% increased risk of death at 180 days (hazard ratio, 1.08; \(p = 0.03\)) (Fig. 1).

Fortunately, techniques to treat pain and anxiety while maintaining wakefulness and preventing systemic drug accumulation have been developed and carefully studied in ICU patients. Sedation scales and protocolized sedation regimens, in particular, have been shown to decrease sedative exposure, patient discomfort, and time on mechanical ventilation (4–7). Both daily interruption of sedative medications and strategies targeting light levels of sedation (both shown to improve patient outcomes in randomized trials) are supported by the recently updated Society of Critical Care Medicine (SCCM)/American Society of Health-System Pharmacists guidelines for the management of pain, agitation, and delirium in the ICU (1). The purpose of this article is to compare and contrast daily sedative interruption with targeted sedation strategies in critically ill patients.

**DISCUSSION**

**Daily Sedation Interruption**

The use of continuous sedative infusions to reduce arousal levels (often measured using validated sedation scales, for example, the RASS [3] or the Sedation-Agitation Scale [SAS] [8]) is common in the treatment of ICU patients, but continuous use of these infusions rather than intermittent delivery of sedatives has been associated with longer durations of mechanical ventilation, ICU stays, and hospital stays (9). Kress et al (10) studied the effects of interrupting continuous sedative infusions, an approach often referred to as a spontaneous awakening trial (SAT), in a randomized controlled trial of 128 medical ICU patients receiving mechanical ventilation and continuous infusions of sedative agents. Protocolized sedation was performed with either midazolam or propofol infusions titrated to target a Ramsay Sedation Scale (11) of 3 or 4 (responsive to verbal commands or light stimulation) in both study groups. In the intervention group, sedative infusions were interrupted on a daily basis (except when neuromuscular blockade was being used) until patients were awake or became uncomfortable, whereas the control group had sedation interrupted only at the discretion of the clinicians. In this trial, daily interruption of sedation decreased median duration of mechanical ventilation by 2.4 days (\(p = 0.004\)) and median length of ICU stay by 3.5 days (\(p = 0.02\)) when compared with usual care. The percentage of patients requiring neuroimaging in the intervention group was also lower than in the control group (\(p = 0.02\)), whereas no difference was seen in complication rates between the two groups. Although concerns were raised about whether patients would experience adverse psychiatric symptoms due to interruption of sedation, follow-up evaluations of this cohort revealed fewer psychiatric symptoms (as shown by a lower impact of events score and posttraumatic stress disorder prevalence) in patients who received the daily sedation interruption than among those in the control group (12).

**Is Daily Sedation Interruption Appropriate for Every ICU Patient?**

Although the above randomized controlled study demonstrated that daily sedation interruption significantly improved patient outcomes, the results of a survey by Tanios et al (13) indicated that many critical care practitioners are reluctant to implement daily sedation interruption protocols in their ICUs. Perceived barriers included lack of nursing acceptance, concern for device removal, and patient discomfort or respiratory compromise. Despite these concerns, an increasingly large number of hospitals have reported successfully incorporating
daily sedation interruption, as well as other changes in sedation management, into their routine ICU practice. For example, Balas et al (14) implemented a daily SAT protocol in a large tertiary medical center as part of the ABCDE bundle program (Awakening and Breathing Coordination, attention to the Choice of sedation, Delirium monitoring, and Early mobility and exercise) (15) and found that three of every four patients underwent SATs. Compared with patients managed prior to the bundle implementation, those managed with this program spent more days breathing without ventilator assistance ($p = 0.04$) and had fewer days with delirium ($p = 0.004$).

Although the evidence suggests that every patient sedated in the ICU should be assessed to determine whether daily sedation interruption should be performed, important patient subgroups may not benefit from this approach to sedation management. Neuromuscular blockade, symptoms of alcohol withdrawal, and ongoing agitation are all indications to continue rather than interrupt sedation in these patients. One trial compared daily sedation interruption with a protocolized sedation algorithm in a population of mechanically ventilated medical patients known to have a high rate of alcohol withdrawal (16). The daily sedation interruption group had sedation management at the discretion of the ICU clinicians and did not use specific nursing-driven protocols (such as safety screens and measures) for the sedation administration or the sedation interruption, whereas the nursing-implemented sedation algorithm was well known to the nursing staff and designed to specifically address pain and agitation while minimizing continuous sedative infusions. The study was terminated prematurely when an interim analysis found patients in the daily sedation interruption group had a longer duration of mechanical ventilation than those in the sedation algorithm group. The authors suggested a high rate of alcohol withdrawal disorders in their patient population may have contributed to their results; thus, sedation of such patients should be managed cautiously.

### Coordinating Sedation Interruption With Spontaneous Breathing Trials

Daily interruption of sedation may be most effective when coordinated with daily spontaneous breathing trials (SBTs). In randomized controlled trials of mechanically ventilated ICU patients, SBTs have been shown to improve ICU outcomes (e.g., reduced ventilator days, weaning time, reintubation rates) and to reduce costs of care (17, 18). In the Awakening and Breathing Controlled (ABC) Trial, Girard et al (19) explored the benefits of pairing daily sedation interruption with SBTs in a randomized controlled study of 336 mechanically ventilated medical ICU patients. Patients were randomized to receive either SATs paired with subsequent SBTs or sedation per usual care plus daily SBTs. Both groups were managed by protocolized targeted sedation with benzodiazepines, propofol, and/or opioids (medication choice was left to the primary ICU clinicians) titrated to maintain arousal levels deemed appropriate by the clinical team. Compared with those in the control group, patients in the intervention group receiving the SAT/SBT paired trials experienced a 3-day increase in ventilator-free days over the 28-day study period ($p = 0.02$), as well as a decrease in median ICU and hospital length of stay by 3.8 ($p = 0.01$) and 4.3 days ($p = 0.04$), respectively. Although patients in the SAT/SBT group were more likely to self-extubate (9.5% vs 3.6%), this did not result in a difference in reintubation rates between the two groups (13.8% vs 12.5%). Finally,
patients in the SAT/SBT group had improved survival rates at 1 year (hazard ratio for death, 0.68; \( p = 0.01 \)) with a number needed to treat to save one life of only 7.4 patients (Fig. 2). Patients at the largest enrolling site of the ABC study (\( n = 180 \)) were evaluated 3 and 12 months after discharge for cognitive, psychological, and functional outcomes, and no long-term adverse outcomes were associated with being managed with the paired SAT/SBT protocol (20).

### Targeted Light Sedation

Sedation protocols designed to target specific arousal levels have been shown to improve patient outcomes and cost (5–7, 21–28). Most of these protocols specifically targeted a light level of sedation, suggesting that an arousal target of light sedation is most likely to improve patient outcomes from critical illness. In the first randomized trial to examine targeted sedation, Brook et al (6) compared physician-ordered sedation with a protocol that prioritized analgesia, discouraged the use of sedative infusions, and used the Ramsay Sedation Scale to titrate sedative doses to achieve a moderate level of sedation (e.g., Ramsay 3). Compared with patients whose sedation could only be changed by physician order, those managed with the sedation protocol spent 1.2 fewer days on the ventilator (\( p = 0.003 \)), 1.8 fewer days in the ICU (\( p = 0.01 \)), and 4.9 fewer days in the hospital (\( p < 0.001 \)). In a subsequent trial by Treggiari et al (28), 137 mechanically ventilated medical and surgical ICU patients were randomized to receive either light (Ramsay 1–2) or deep (Ramsay 3–4) targeted levels of sedation. Light sedation was achieved with intermittent injections of midazolam, whereas deep sedation was achieved with continuous infusions of midazolam. Daily sedation interruption was not mandated, and patients received standardized ventilator weaning. Patients receiving sedation at the lighter target were found to have a decrease in the median duration of mechanical ventilation by 2.6 days (\( p = 0.02 \)), an increase in median ventilator-free days by 0.9 days over 7 days (\( p = 0.02 \)), a decrease in ICU length of stay by 1.5 days (\( p = 0.03 \)), and an increase in ICU-free days of 3 days (\( p = 0.03 \)). There were no significant differences in self-extubation or reintubation rates in this study. At 4-week follow-up, patients in the light sedation group had less difficulty with memory, fewer disturbing memories of the ICU, and fewer posttraumatic stress disorder symptoms (28). These results are consistent with studies that have demonstrated that ICU sedative utilization and days of sedation are associated with posttraumatic stress disorder and depression (29) and that patients with complete amnesia of their ICU stay have increased rates of cognitive sequelae at hospital discharge and 1-year follow-up (30).

A number of additional trials have compared analgesia-based sedation regimens (i.e., analgosedation) versus traditional moderate/deep sedation. Strom et al (31) conducted a trial of 140 medical and surgical ICU patients requiring mechanical ventilation and randomized them to receive analgesia-based “no-sedation” with a morphine-based protocol versus propofol or midazolam sedation (with daily interruption of sedation) targeting a Ramsay score of 3–4. Patients receiving the analgesia-based protocol had 4 more days without ventilation (\( p = 0.02 \)) over a 28-day period, approximately 10 fewer days in the ICU (\( p = 0.03 \)), and 24 fewer days in the hospital (\( p = 0.004 \)). However, agitated delirium occurred more frequently in the intervention group than in the control group (20% vs 7%, \( p = 0.04 \)). No differences were observed in the prevalence of accidental extubation, neuroimaging, or ventilator-associated pneumonia between the two groups. The prolonged lengths of stay, relatively high mortality rates, and 1:1 nursing ratios in the ICU with other personnel available to reassure patients decrease the generalizability of this study to other institutions. It is important to note, however, that approximately 80% of the patients in the intervention group were managed with morphine alone, demonstrating that pain control and frequent communication with reassurance may be sufficient therapy without additional sedative use for a large percentage of ICU patients. The results of this trial are also consistent with other studies comparing the use of analgesia-based regimens with moderate/deep sedative regimens in ICU patients, which have demonstrated that analgesia-based regimens can significantly shorten the duration of mechanical ventilation and ICU length of stay in these patients (32–34).

### Combining Daily Sedation Interruption With Targeted Light Sedation

To date, only one study has addressed whether daily sedation interruption provides additional benefit when combined with a preexisting protocol targeting light sedation. Mehta et al (35) conducted a multicenter randomized controlled trial of 430 mechanically ventilated medical and surgical ICU patients, comparing protocolized light sedation in combination with daily sedation interruption versus protocolized light sedation alone (SLEAP trial). In both groups, ICU nurses titrated analgesic and sedative (midazolam or lorazepam) infusions according to a protocol that emphasized pain assessments and targeted light levels of sedation (i.e., a RASS of –3 to 0 [3] or a SAS of 3–4 [8]). Ventilator weaning was at the discretion of the ICU team, and SBTs were performed in both groups once specified criteria were met; SBTs, however, were not paired with sedation interruption in the combination group. In contrast to the results of earlier studies in which daily sedation interruption markedly reduced exposure to sedatives, patients in the combination treatment group of the SLEAP trial received significantly higher doses of sedatives (\( p = 0.04 \) for benztropine equivalents) and opioids (\( p < 0.001 \) for fentanyl equivalents) and a greater number of IV boluses of sedatives (\( p = 0.007 \) for benzodiazepine equivalents) and opioids (\( p < 0.001 \) for fentanyl equivalents) than patients managed without sedation interruption. Sedation interruption occurred on only 72.2% of eligible days in the combination group, with the majority of protocol noncompliance secondary to mechanical ventilation issues, agitation, or pain. Nurse-reported workload was higher in the combination group (\( p = 0.001 \)), whereas respiratory therapist workload and compliance with SBTs were similar between groups. Overall, no difference was found between the groups with regard to time to extubation, duration of ICU stay, hospital length of stay, or self-extubation. Among the surgical and trauma patients, daily sedation interruption...
Exposure to benzodiazepines contributes to the improved outcomes seen in protocolized sedation, daily sedation interruption, and targeted light sedation trials. However, the intervention group in these trials did not have a significant reduction in sedative administration per day. These results suggest that decreasing benzodiazepine exposure in their intervention groups. Bucknall et al (41) and Mehta et al (35) did not show a difference in patient outcomes; ventilation duration, ICU length of stay, and mortality) by using either daily sedation interruption or targeted lighter levels of sedation, which significantly decreased benzodiazepine exposure in their intervention groups. Kress et al (10), Girard et al (19), Treggiari et al (28), and Strom et al (31) were able to demonstrate improvement in patient outcomes (including mechanical ventilation duration, ICU length of stay, and mortality) by using either daily sedation interruption or targeted lighter levels of sedation, which significantly reduced benzodiazepine exposure in their intervention groups. Kress et al (10), Girard et al (19), Treggiari et al (28), and Strom et al (31) did not show a difference in patient outcomes; however, the intervention group in these trials did not have a significant reduction in sedative administration per day. These results suggest that decreasing exposure to benzodiazepines contributes to the improved outcomes seen in protocolized sedation, daily sedation interruption, and targeted light sedation trials.

A major limitation of the SLEAP trial is lack of clear evidence that daily sedation interruption was successfully implemented. Although daily compliance with sedation interruption was reported to be 72.2%—a result significantly lower than that observed in previous studies which performed daily sedation interruption on greater than 90% of eligible study days (10, 19)—significantly higher sedative doses were delivered to the daily sedation interruption group than to the group managed without sedation interruption, suggesting that the interruption of sedation may have been brief and accompanied by additional bolus doses of sedatives. The lack of a safety screen to determine which patients should have their sedation turned off may have also contributed to the need for additional sedation in patients who otherwise would have been disqualified from sedation interruption trials. The results from the SLEAP study conflict with those of two previous randomized trials (10, 19) and a recent implementation study (14) finding that sedation interruption reduced exposure to sedatives and led to improved outcomes. The perceived increase in nursing workload with the daily sedation interruption found in the SLEAP trial may have contributed to this reduced adherence and effectiveness; the improved outcomes achieved by sedation interruption in the trials by Kress et al (10) and Girard et al (19) are most likely to occur when adherence is good and sedative doses are reduced. A potential benefit of pairing SBTs with sedation interruption is that the ICU team may be more willing to do without unneeded sedation when the possibility of extubation is apparent, that is, when the patient is undergoing a SBT.

Another shortcoming of the SLEAP study was that mean SAS score for both groups was 3, indicative of moderate sedation levels. Thus, although it is unclear from the article as to how often patients were in the target sedation range, periods of deep sedation were likely common. The sedative doses administered were also likely to have resulted in a high prevalence of moderate to deep sedation in both groups. Specifically, the treatment and control groups received average sedative doses (midazolam equivalents) of 4.2 mg/hr and 3.4 mg/hr, respectively, and opioid doses (fentanyl equivalents) of 74 µg/hr and 45 µg/hr, respectively. Based on pharmacologic models, this would result in moderate to deep levels rather than light levels of sedation (36).

A consistent finding across all trials of daily sedation interruption and/or targeted light sedation is that clinical outcomes are improved when sedative doses are significantly reduced, but outcomes remain unchanged when sedative doses are not reduced. Table 1 demonstrates the difference in benzodiazepine exposure, for example, in several of the studies described. In the studies that achieved lower benzodiazepine exposure in the intervention group, the intervention (either daily interruption of sedation or targeted lighter levels of sedation) was associated with improved patient outcomes. In contrast, in studies that did not achieve lower benzodiazepine exposure in the intervention group, the intervention resulted in “no difference” in outcomes.

Another issue that may influence clinical outcomes in these studies is sedative choice. Most trials of sedation management

### Table 1. Benzodiazepine Exposure in Selected Sedation Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>Intervention</th>
<th>p</th>
<th>Improved Outcomes?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kress et al (10)</td>
<td>58 mg/d</td>
<td>47 mg/d</td>
<td>0.05</td>
<td>Yes</td>
</tr>
<tr>
<td>Girard et al (19)</td>
<td>84 mg/d</td>
<td>54 mg/d</td>
<td>0.02</td>
<td>Yes</td>
</tr>
<tr>
<td>Bucknall et al (41)</td>
<td>67 mg/d</td>
<td>64 mg/d</td>
<td>0.49</td>
<td>No</td>
</tr>
<tr>
<td>Treggiari et al (28)</td>
<td>54 mg/d</td>
<td>7 mg/d</td>
<td>Not reported</td>
<td>Yes</td>
</tr>
<tr>
<td>Strom et al (31)</td>
<td>6 mg/d</td>
<td>0 mg/d</td>
<td>&lt; 0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Mehta et al (35)</td>
<td>82 mg/d</td>
<td>102 mg/d</td>
<td>0.04</td>
<td>No</td>
</tr>
</tbody>
</table>

*All values converted to and expressed as median midazolam exposure per patient receiving benzodiazepines.

*Protocalized sedation, daily sedation interruption, or targeted lighter level of sedation.

Kress et al (10), Girard et al (19), Treggiari et al (28), and Strom et al (31) were able to demonstrate improvement in patient outcomes (including mechanical ventilation duration, ICU length of stay, and mortality) by using either daily sedation interruption or targeted lighter levels of sedation, which significantly decreased benzodiazepine exposure in their intervention groups. Bucknall et al (41) and Mehta et al (35) did not show a difference in patient outcomes.
in the ICU have typically included the use of benzodiazepines, which are the most commonly administered sedatives in ICU patients and were the primary class of sedatives recommended in the 2002 version of the ICU sedation and analgesia guidelines (38). More recent evidence summarized in a meta-analysis included in the 2013 guidelines for the management of pain, agitation, and delirium compared ICU outcomes based on sedative choice and showed that the use of benzodiazepines is associated with longer ICU length of stay than sedation with nonbenzodiazepines (i.e., propofol or dexmedetomidine). An updated and expanded version of this benzodiazepine versus nonbenzodiazepine sedation meta-analysis published by Fraser et al (39) in this supplement also demonstrates a longer duration of mechanical ventilation with benzodiazepine sedation.

Sedative choice may, therefore, influence ICU outcomes in addition to overall sedative exposure in these patients, which can confound interpretation of results across studies. Temporarily reducing sedative concentrations in the brain through daily sedative interruption, however, may also influence patient outcomes. Patients receiving propofol in sedation interruption studies (10, 19), for example, did not receive significantly less propofol (or other sedatives) when managed in the sedation interruption group, but these patients still had improved outcomes compared with those in control groups, suggesting there may be benefits from the performance of sedation interruption in addition to those attributed to reductions in total sedative dose. Whether these results hold true for patients sedated with dexmedetomidine has not been studied, although the association of early deep sedation with delayed extubation and higher mortality found in a recent observational study was irrespective of sedative medication regimen (40). Importantly, neither daily sedation interruption nor targeted light sedation has been associated with adverse safety outcomes in the ICU, and both methods may actually decrease long-term adverse psychiatric outcomes, such as posttraumatic stress disorder (12, 20).

CONCLUSIONS

Despite their clinical usefulness in the ICU, exposure to sedative medications can worsen patient outcomes, especially in ICU patients who are deeply sedated. Daily sedation interruption and continuously targeting light sedation levels are both effective strategies for reducing exposure of critically ill patients to sedative medications and for improving ICU patient outcomes. Contrary to conventional wisdom, these sedation strategies have not been associated with an increased prevalence of psychiatric disturbances in ICU patients. Although some studies have shown a higher prevalence of self-extubation at lighter levels of sedation, the prevalence of reintubation has also not been higher in patients maintained at lighter levels of sedation. In contrast, deep sedation in these patients has been associated with increased mortality and shown to result in a higher prevalence of acute delirium and post-ICU cognitive dysfunction and posttraumatic stress disorder symptoms. Although daily sedative interruption and targeting light levels of sedation are both associated with improved ICU outcomes, it remains unclear as to whether one approach is better than the other. For this reason, the 2013 Pain, Agitation, and Delirium Clinical Practice Guidelines recommend using either daily sedative interruption or targeted sedation strategies in order to maintain lighter levels of sedation in critically ill patients and to improve their clinical outcomes (1).

The benefits of both of these techniques may lie in the minimization of patient exposure to sedative agents and avoidance of deep sedation. Combining targeted light sedation with daily sedation interruption may be more beneficial than either method alone if this results in a further decrease in drug exposure and lighter levels of consciousness that allow for patients to actively participate in SBIs, early mobility programs, and delirium assessments. The only published study to date which combines daily sedation interruption with a protocol targeting light sedation resulted in a paradoxical increase in sedative exposure and worse clinical outcomes in the combined treatment group. Further studies are needed to address this issue.

Widespread use of deep sedation in critically ill patients is a significant barrier to optimizing ICU patient care. ICU protocols that optimize pain management, minimize the use of sedatives in order to maintain a light level of sedation, and detect and manage delirium enable ICU patients to actively participate in ventilator weaning and early mobility and can significantly improve ICU patient outcomes. The ICU PAD care bundle which is included in the SCCM’s 2013 clinical practice guidelines (1) provides an integrated approach to managing pain, agitation, and delirium and advocates for maintaining light levels of sedation using either daily sedative interruption or targeted sedation strategies.

REFERENCES


