Why Sedation Liberation and ICU Mobility Are Important in Outcomes and Costs

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Objectives

- Describe short- and long-term outcomes associated with current sedation liberation practices
- Review clinical outcomes associated with early mobility during critical illness
- Explore the financial costs associated with sedation liberation and ICU mobility

Key words: sedation liberation, early mobility, benzodiazepines, propofol, dexmedetomidine, daily interruption of sedation, Awake and Breathing Coordination, physical rehabilitation, clinical outcomes, ICU

What I see these days are paralyzed, sedated patients, lying without motion, appearing to be dead, except for the monitors that tell me otherwise. Why this syndrome of sedation and paralysis has emerged baffles me, because this was not always the case in the past…When we first started our [intensive care unit] in 1964, patients who required mechanical ventilation were awake and alert and often sitting in a chair…By being awake and alert, these individuals could interact with their family, friends and the environment. They could feel human. By so doing, they could sustain the zest for living, which is a requirement for survival.

— Dr Thomas L. Petty, MD

In many ways the face of critical care medicine has changed dramatically since Dr. Petty, one of the fathers of modern critical care medicine, penned those words nearly 2 decades ago. Today, more patients than ever are developing critical illness and are being admitted to ICUs. Advances in research and clinical ICU care mean that more of these patients than ever are surviving their illness. Survivorship, however, is often complicated by persistent physical, cognitive, and psychological impairments. These impairments, which were not suffered by previous generations of critically ill patients because they did not survive, dramatically alter the lives of those who survive a critical illness and their families for years afterwards.

As an understanding of the burdens of survivorship has come to light, clinicians and researchers alike have begun to explore how the nearly ubiquitous ICU management practices of deep sedation and immobility that Dr. Petty described may be related to these poor long-term outcomes. While these practices can be beneficial in some clinical settings, the harms associated with them are now clear. In today’s busy ICU environment, however, many clinicians remain so focused on the hour-to-hour and day-to-day management of their increasingly sick and complex patients—with many clinicians feeling overwhelmed by these demands—that they fail to understand the long-term consequences of the care they deliver.
In this chapter we review the short- and long-term clinical outcomes associated with sedation liberation, the foundation of the 2013 pain, agitation, and delirium (PAD) clinical practice guidelines. We also discuss the positive clinical outcomes associated with early mobility during critical illness. Finally, we consider the economic implications of these practices in reducing ICU costs.

SEDATION LIBERATION

The use of sedation in the ICU stems from our humanitarian desire to relieve suffering and to prevent the potentially harmful consequences of agitation for patients and those caring for them. Yet, for unclear reasons, it became common belief that patients need to be deeply sedated and completely detached from the environment. Several lines of evidence now support the importance of minimizing exposure to sedatives in the ICU in order to improve patient outcomes, and the emerging theme of modern ICU sedation practice is “less is more.”

A number of protocols exist to aid in liberating patients from sedation, and each is associated with better patient outcomes. As a result of these studies and others, ICUs are increasingly adopting protocolized approaches to sedation in critically ill patients. While sedation protocols vary from one ICU to another, common themes that run throughout each include administering analgesics prior to administering sedatives, using intermittent (bolus) doses of opiates and sedatives when possible, using nonbenzodiazepine sedation regimens, frequently assessing level of consciousness (using a validated sedation-agitation scale) so that light levels of sedation (rather than moderate or heavy) may be targeted, and interrupting opiate and sedation administration each day. Herein, we review the short- and long-term outcomes associated with each of these sedation liberation strategies. The specifics of how best to implement these sedation liberation strategies are discussed elsewhere in this book.

Administering Analgesics Before Sedatives

Pain is common among critically ill patients and a common reason for agitation; thus, assessing and treating pain may be sufficient to reduce agitation and restore a patient to a calm state. In several studies, treating pain prior to administering sedatives was associated with improved outcomes including shorter duration of mechanical ventilation and shorter ICU and hospital lengths of stay.

Perhaps the most illustrative example of this approach comes from a Danish study examining patients randomized to a protocol of “no sedation” compared with patients receiving continuous sedation, titrated to a light level, with daily sedation interruption. Patients in the “no sedation” group who were agitated were first given morphine to treat pain, and if they remained agitated, were given haloperidol. Then, only if their agitation persisted, were they administered a 6-hour course of continuous sedation with propofol. Patients who were randomized to the no-sedation group spent significantly less time on mechanical ventilation and were discharged from the ICU nearly 10 days earlier than those receiving a conventional sedation strategy (continuous propofol plus daily interruption) (Figure 1). In addition to supporting the notion that treating pain is an effective way to reduce agitation in the ICU, data from this trial showed that only 1 in 5 patients being managed with the no-sedation protocol ever required continuous sedation (i.e., for >6 hours), challenging the common assumption that sedation is a necessity for mechanically ventilated patients.

Using Intermittent Sedation

While continuous administration is the most common method of providing sedation in the ICU, a second way to liberate patients from sedation is to use intermittent (bolus) sedation. Intermittently administered medications have several benefits over continuous infusions. First, continuous infusions are more likely to result in accumulation of the infused drug, which may result in prolonged effects and delayed drug clearance. Second, continuous infusions are readily titrated up to treat acute agitation but rarely are titrated back down once the acute agitation is resolved. Combined, these factors typically result in an overall greater exposure to sedative medications in patients managed with continuous infusions.
In addition to the improved outcomes among patients receiving no sedation who were treated with intermittent morphine and haloperidol, discussed above, data supporting this approach are also derived from a second study of 242 mechanically ventilated patients randomized to receive either continuous or intermittent doses of benzodiazepines. Patients in this study who were managed with intermittent dosing were extubated and discharged from the ICU and hospital sooner than those who received continuous dosing.

Using Nonbenzodiazepine Regimens

Over the last 30 years, a number of clinical trials have demonstrated improved outcomes among patients who were managed with nonbenzodiazepine sedation regimens. Yet a number of these early studies were limited by the fact that they used continuous infusions of benzodiazepines rather than intermittent administration. To address this gap in knowledge, Carson and colleagues examined intermittent administration of benzodiazepines compared with continuous infusion of propofol in a 132-patient randomized trial. In both groups, adequate analgesia was provided, sedation was titrated to a light level, and medications were interrupted daily. Patients who were managed with intermittent lorazepam had worse outcomes and spent significantly more days on the ventilator than those who received continuous propofol.

Most recently, a much larger study examined outcomes among patients who were sedated with benzodiazepines (i.e., lorazepam or midazolam) compared with patients sedated with propofol. This retrospective study used propensity scoring statistical techniques to match subjects according to a number of important clinical features, including age, sex, reason for ICU admission, year of ICU admission, chronic health conditions, and pre-illness functional status. Both cohorts of patients who were sedated with benzodiazepines had significantly longer ICU and hospital lengths of stay, spent more days on mechanical ventilation, and most notably, were more likely to die in the ICU compared with those patients who were sedated with propofol (Figure 2).

Benzodiazepines have also been compared with newer sedative agents, including dexmedetomidine and remifentanil. Seven trials, enrolling a total of 1,562 mechanically ventilated patients, have examined the use of benzodiazepines compared with dexmedetomidine, and all 7 trials reported...
worse outcomes including greater delirium and longer duration of mechanical ventilation in patients managed with benzodiazepines.20-26 Similarly, 3 trials (N = 290) have compared remifentanil-based sedation strategies to benzodiazepines. Patients receiving benzodiazepines demonstrated worse outcomes, including more time on mechanical ventilation and longer ICU length of stay.27-29

To date, no study has reported improved outcomes among patients sedated with benzodiazepines.16

**Targeting Light Sedation and Interrupting Sedative Administration Daily**

While each of the above methods to liberate patients from sedation is associated with improved outcomes, perhaps the most important step is to reduce the overall exposure to sedatives, regardless of the sedative agent used. Evidence-based methods to reduce sedative exposure include sedating patients only to the point where they are no longer agitated (i.e., light sedation) and holding sedatives each day to ensure they are still needed (i.e., daily interruption of sedation).

In a randomized trial comparing targeted deep sedation (e.g., patient awakening only to physical stimulation) and targeted light sedation (e.g., patient awake and cooperative), patients who were managed with light sedation spent significantly less time on the ventilator and were discharged from the ICU sooner.30

The outcomes associated with light sedation were also evaluated in 2 large multicenter observational trials.31,32 In both trials, deep sedation within the first few hours of mechanical ventilation was common, occurring in 3 of 4 patients, and, as with prior studies, was associated with a longer duration of mechanical ventilation. Most importantly, even after adjustment for potential confounders of mortality, deep sedation was independently associated with an increased risk of mortality 6 months later, such that every 4 hours a patient was unarousable to voice the risk of death increased by nearly 10%.
Even when light sedation is targeted and intermittent doses are used, sedatives and opiates should be held each day so that clinicians can assess the need for these agents and can determine the optimal doses of opiates and sedatives necessary to maintain patient comfort and alert mental status. This daily interruption of sedatives is also known as sedation vacation, sedation holds, daily wake-up, or spontaneous awakening trial and has been evaluated in 3 randomized clinical trials.6,7,33 The first 2 studies demonstrated significantly shorter durations of mechanical ventilation and shorter ICU stays compared with continuous, uninterrupted sedation.6,7 The lone study to evaluate the long-term outcomes associated with sedation interruption which paired daily sedation interruption with daily spontaneous breathing trials (i.e., the “wake up and breathe” approach), found a significant (14%) reduction in mortality one year after critical illness in patients who underwent daily interruption of sedation (Figure 3).

Finally, a third study evaluated whether daily interruption of sedation combined with targeted light sedation was superior to targeted light sedation alone.33 Patients in this study had similar outcomes, regardless of whether sedation was interrupted. Interestingly, however, sedation interruption actually led to an increased exposure to sedation (i.e., benzodiazepines) whereas in the former 2 studies daily interruption resulted in less exposure. Thus, it may be the case that daily sedation interruption is only beneficial when it is applied in such a manner so as to decrease overall sedative exposure.

In summary, liberating patients from sedation can occur via a number of different methods, including treating pain prior to administering sedatives, using intermittent doses rather than continuous sedation, preferentially selecting nonbenzodiazepine sedation regimens, targeting light (rather than moderate or heavy) sedation, and interrupting sedation each day. These approaches, when they reduce exposure to sedation, are consistently associated with improved clinical outcomes including shorter durations of mechanical ventilation as well as shorter ICU and hospital lengths of stay (Table 1). Sedation with benzodiazepines and deep sedation are associated with greater mortality. A strategy that combines daily sedative interruption with daily spontaneous breathing trials can significantly reduce mortality.

**Early Mobility**

Driven by changes in ICU sedation practices resulting in more awake and alert patients as well as the findings of significant physical morbidity suffered by survivors of critical illness,34,35 researchers began to address the second component of routine ICU care that baffled Dr. Petty, “patients lying motionless.”

For many years, critically ill patients were believed to be too sick to be mobilized. A landmark study published in 2007 by Bailey and colleagues36 challenged the notion that critically ill patients were too
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<th>Sedation Liberation Protocol</th>
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<th>Outcomes Improved</th>
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<tbody>
<tr>
<td>Daily interruption of sedation (Kress et al)</td>
<td>58</td>
<td>47</td>
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<td>Shorter duration of mechanical ventilation</td>
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<td>Daily interruption of sedation plus daily spontaneous breathing trial</td>
<td>84</td>
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<td>Sedation protocol (Bucknall et al)</td>
<td>67</td>
<td>64</td>
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<td>Targeted light sedation (Treggiari et al)</td>
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<td>Similar rates of anxiety and depression</td>
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<td>No sedation (Strøm et al)</td>
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<td>Shorter hospital length of stay</td>
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<td>Targeted light sedation plus daily interruption of sedation (Mehta et al)</td>
<td>82</td>
<td>102</td>
<td>0.04</td>
<td>No improved outcomes</td>
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These data suggest that reductions in sedation exposure, specifically to benzodiazepines, through the use of sedation liberation protocols are consistently associated with improved clinical outcomes including shorter durations of mechanical ventilation, shorter ICU lengths of stay, shorter hospital lengths of stay, and reduced mortality. Conversely, when these protocols fail to reduce exposure to sedation, clinical outcomes are not improved.

*Benzodiazepine dose presented as the mean daily dose, among patients exposed to this class of medications, in midazolam equivalents.*
sick to tolerate physical activity, and the investigators reported the safety and feasibility of early activity in 103 critically ill patients. Of more than 1,400 activity sessions performed, no major complications occurred and patients suffered minor complications such as mild oxygen desaturations or episodic tachycardia in less than 1% of sessions.

Subsequently, Morris and colleagues used a block allocation design to assign 330 mechanically ventilated patients to usual care or to treatment with a dedicated mobility team consisting of a physical therapist, a critical care nurse, and a nursing assistant who used a graded mobility protocol that progressed patients from passive range of motion exercises to ambulation. Patients who were treated by the mobility team received earlier physical therapy, were mobilized out of bed sooner, and had shorter ICU and hospital lengths of stay. Moreover, patients undergoing early mobilization were less likely to die or be rehospitalized in the year following their critical illness.

The largest randomized clinical trial of early mobility was conducted by Schweickert and colleagues, who allocated 104 patients to either physical and occupational therapy beginning during the first 72 hours of mechanical ventilation or usual care (i.e., physical therapy when the clinical ICU team believed the patient was ready). A greater proportion of patients who received early physical and occupational therapy returned to independent functional status at the time of hospital discharge than those who received physical and occupational therapy beginning later in their illness (Figure 4). Patients who received early physical and occupational therapy also had more days alive and free of mechanical ventilation and significantly shorter durations of delirium than patients treated with usual care.

These trials have spawned a number of nonrandomized clinical trials and quality improvement projects that were reviewed in 4 systematic and narrative reviews. Findings from these reviews highlight the heterogeneity of the types of mobility interventions provided, the patient populations in whom early mobility was performed, and the ways outcomes were measured. Nevertheless, they affirm the safety and feasibility of early mobility in critically ill patients.
Moreover, patients who are treated with early mobility, broadly defined, consistently achieve functional milestones (e.g., sitting out of bed, standing, and ambulating) sooner, have more days alive and free of mechanical ventilation, and suffer less physical disability at hospital discharge than those who are not treated with this type of intervention. Additionally, several nonrandomized studies reported shortened lengths of ICU and hospital stays.

In summary, early mobility is an emerging, yet safe rehabilitation modality for patients with critical illness. While the long-term benefits of this intervention are incompletely understood, it is associated with improved short-term outcomes including shorter duration of mechanical ventilation, improved physical functioning, reductions in disability, and shorter lengths of stay.

Costs Associated With Sedation Liberation and Early Mobility

A commonly cited barrier to implementing sedation liberation and early mobility is the perceived costs of these interventions. The drug acquisition costs of benzodiazepines, for example, are lower than those of dexmedetomidine or propofol, justifying for some the continued use of benzodiazepines as first-line agents. Mobilizing patients from bed potentially requires additional resources in the form of personnel (who require training, salaries, and benefits) as well as specialized equipment (e.g., portable ventilators, wheelchairs) that make this intervention seemingly cost prohibitive. Nevertheless, a growing number of studies report that the improved outcomes such as shorter durations of mechanical ventilation and of ICU length of stay derived from sedation liberation and ICU mobility either offset these costs or even result in cost reductions.

Jackson and colleagues conducted a systematic review of the impact of sedation protocols on resource utilization. They reviewed 7 studies that reported data on the effect of sedation protocols on costs and found that in each study, the cost of sedative agents when sedation protocols were used was equal to or lower than costs when such protocols were not used, perhaps driven by a reduction in the overall duration of sedation and doses of sedatives administered to patients in the protocolized groups.

Three studies have specifically compared costs of sedation with benzodiazepines versus sedation with nonbenzodiazepine agents, considering not just the drug acquisition costs but the overall cost of an ICU stay. Dasta and colleagues performed a pharmacoeconomic evaluation using data from the Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) trial to determine the overall ICU cost difference between patients sedated with dexmedetomidine compared with those sedated with midazolam. Although drug acquisition costs were nearly 60 times greater for dexmedetomidine, ICU costs among patients sedated with this drug were an average of $10,000 less than the ICU costs for patients sedated with midazolam, primarily driven by the shorter duration of mechanical ventilation and ICU length of stay seen in the dexmedetomidine group. A similar (but smaller) reduction in costs was found when the SEDCOM data were applied to a Canadian cohort.

Finally, cost-effectiveness of benzodiazepine-sparing regimens was evaluated using data from a meta-analysis of clinical trials that compared sedation using benzodiazepines versus nonbenzodiazepine agents. While the overall drug acquisition costs were higher for nonbenzodiazepine regimens, sedation with these agents was associated with a significant reduction in ICU costs, primarily driven by a shorter duration of mechanical ventilation and ICU length of stay among patients managed with nonbenzodiazepine agents.

Using cost data collected during the implementation of a physical rehabilitation program in the medical ICU at Johns Hopkins Hospital, Lord et al modeled the financial savings and costs associated with implementing an early mobility program. The authors reported that after accounting for costs associated with personnel, training, and equipment, implementation of an early mobility program at their institution was associated with a net annual cost savings of $817,836, with a majority of the savings realized through reductions in ICU length of stay. Then, to provide other ICUs with an estimate of savings (or potential costs) they may incur by implementing a similar program,
the authors performed a series of sensitivity analyses across a range of ICU sizes, expected reductions in length of stay, and variable direct costs associated with ICU care (i.e., those pertaining to laboratory, pharmacy, radiology, and others). Among the 24 scenarios evaluated, implementing an early mobility program was associated with a cost savings in 20 scenarios. The financial impact estimated in these scenarios ranged from a net annual savings of $3.7 million to a net cost of $88,000.

These studies illustrate the positive financial outcomes that may be achieved through the implementation of evidence-based practices of sedation liberation (reducing sedative exposure and using nonbenzodiazepine sedatives) and early mobility. Cost, in and of itself, should not be a barrier to implementing these strategies, which are also clearly linked with improved short- and long-term patient outcomes.

SUMMARY

Survivorship has been called the “defining challenge of critical care in the 21st century.” The role of deep sedation and immobility in poor outcomes for survivors of critical illness is becoming clear. Yet these harmful practices remain common. We must, as Dr. Petty reminds us, return to our roots and avoid deep sedation and immobility, whenever possible. Liberating patients from the harms of sedation and bed rest—by treating pain first, using intermittent dosing when possible, avoiding benzodiazepines, ensuring that our patients are alert and comfortable, evaluating the need for sedatives each day, and mobilizing our patients soon after ICU admission—is a cost-effective, evidence-based means by which to reduce the short- and long-term sequelae of critical illness.

REFERENCES


