Sedation and Neuromuscular Blockade in the ICU

Among the key innovations of critical care medicine is treatment directed by continuously measured objective physiologic data. A prime example is the dosing of vasopressors using continuous measurements of systemic arterial pressure acquired from an indwelling arterial catheter. Similarly, the settings of mechanical ventilators are based on pressure and volume measurements of airway gases and arterial blood gas analysis. However, not all of the care provided in ICUs is so carefully monitored and titrated. This is especially true concerning sedation and analgesia, which are widely used in ICUs, as reported in this issue of CHEST (see page 496), by Arroliga and colleagues. These investigators analyzed data from a prospective, multicenter, international cohort of 5,183 adult ICU patients who received mechanical ventilation for \( 12 \) h in 361 ICUs. Sixty-eight percent of these patients received sedation while being mechanically ventilated, while 13% also received a neuromuscular blocker for at least 1 day. The latter patients had a 50% mortality rate. The sedated patients had longer durations of mechanical ventilation, weaning time, and ICU stays than nonsedated patients. These results are not unexpected since patients receiving sedation and neuromuscular blockade tend to be the most severely ill. However, there is always the lingering question as to whether sedation, analgesia, and administration of neuromuscular blockers contribute to the morbidity and mortality of such patients or are only indications of severe illness.

Critical ill patients are constantly subjected to noxious stimuli, unpleasant experiences, and pain. They require sedatives, amnestics, and analgesics to reduce anxiety and suffering, to control pain, and to manage agitation. Despite the frequent use of these pharmacologic modalities, there is a lack of consensus as to the following: (1) when to administer these drugs, (2) which drugs to administer, (3) the depth of sedation required, and (4) how to monitor the depth of sedation and adequacy of analgesia. This lack of consensus is occasioned by the absence of well-designed and conclusive studies examining these issues. Additionally, there are relatively few studies examining when and how to use neuromuscular blocking agents in critically ill patients.

Much of the knowledge and many of the drugs used to sedate, reduce pain, and pharmacologically paralyze patients in the ICU have been adapted from the operating room environment. However, there are many differences between the critical care and operating room environments that make it difficult to transfer these experiences. In the operating room, there is usually the need for short-term deep anesthesia, amnesia, and total immobility in the face of intensely painful and noxious stimulation. This requires high doses of very potent, relatively short-acting drugs and, frequently, the use of muscle relaxants. This situation differs considerably from the ICU where there is a need for long-term sedation (rather than anesthesia) in patients who frequently have multiple organ system failure and hemodynamic instability. Total immobilization is only rarely needed. Ideally, ICU patients should receive the minimum amount of sedation (ie, sufficient sedation and analgesia for them to be pain free and to tolerate noxious stimuli [eg, endotracheal tubes and suctioning]) while still being safely arousable when stimulated. This is a tall order, considering the ever-changing clinical conditions and degrees of stimulation when patients can rapidly go from being asleep to undergoing chest physical therapy, which is a rather uncomfortable treatment. These situations require the ability to rapidly change the levels of sedation and analgesia to prevent oversedation and undersedation while still maintaining hemodynamic stability. However, instead of a titration approach to sedation, similar to that used for BP control, there is often an extrapolation of the operating room experience to the ICU, which may result in oversedation, deep paralysis, and additional hemodynamic instability. Continuous sedation has been associated with prolonged mechanical ventilation and longer hospital and ICU stays. Moreover, it is recommended that sedation be interrupted daily to permit the evaluation of the patient’s neurologic and respiratory functions. Such an approach leads to a reduction in the duration of mechanical ventilation and ICU stay.
Prolonged sedation, especially with neuromuscular blockade, is especially problematic because it increases the threat of immobilization-related complications, the most serious of which is critical care myopathy.\(^7\)

Much improvement is required in the application and monitoring of sedation, analgesia, and muscle relaxation in critically ill patients. The indications and goals for using these drugs need better definition, especially which drugs to use for which specific purposes. The advent of very short-acting sedatives and analgesics, such as propofol and remifentanil, may make it easier to titrate the depth of sedation. Furthermore, as in the operating room, the critical care arena lacks objective, accurate, reliable, and reproducible ways to monitor the depth of sedation and the effectiveness of analgesia. One approach has been to refine observer-rated (ie, nurse) sedation/agitation scores. These methods involve nurses using a scoring system to evaluate the degree of sedation.\(^8,9\) However, these scales do not provide continuous measurements of the depth of sedation and are subject to intraobserver and interobserver variability. In addition, investigators have pointed out that although these scores examine the degree of sedation, they generally do not evaluate whether the patient is coherent or delirious, or in pain. This limits the usefulness of these scores because it is often not possible to know whether the lack of effective sedation is due to delirium or pain.\(^10\) Simultaneously, there has been increased interest in the use of electrophysiologic measures, such as processed EEG and auditory-evoked potentials, to monitor the level of sedation.\(^11\)–\(^13\) This interest is based on the realization that the intuitive approach to gauging the depth of sedation is to monitor the brain directly. Moreover, because of the complexity of the brain, along with our limited understanding of consciousness, this remains a daunting challenge. However, the electrophysiologic methods are still in their infancy and need to be further developed before they are ready for routine use.\(^14\) Both monitoring techniques and the use of pharmacologic agents need further refinement, as does their integration in the clinical arena (ie, the use of the monitoring modalities to direct the sedation/analgescia).

The use of muscle relaxants in the ICU remains a problematic issue, especially since the indications for the pharmacologic paralysis of ICU patients are unclear. The current recommendations are that muscle relaxants be used to facilitate mechanical ventilation in patients in whom sedation alone is inadequate in providing conditions for effective mechanical ventilation.\(^15\) The use of especially discomforting modalities, specifically the prone position, permissive hypercapnia, and high positive end-expiratory pressure levels, is among the reasons that these drugs are employed. However, as pointed out previously, these drugs, if used excessively, can cause harm. The most basic problem is the creation of a paralyzed but inadequately sedated patient, so it is always important to assess whether muscle relaxation is a substitute for sufficient sedation and to ensure that paralyzed patients receive adequate sedation. Additionally, there is the question of the dosing requirements (ie, whether neuromuscular transmission needs to be completely or only partially abolished).\(^16\) Unlike sedation, it is possible to objectively monitor the depth of neuro muscular relaxation using a peripheral nerve stimulator and to then adjust the strength of the neuromuscular blockade. However, some investigators\(^17\) have questioned the usefulness of such monitoring, especially when short-acting agents are used.

In conclusion, sedation and pain control in critically ill patients are areas of critical care medicine that urgently need further investigation. The widespread use of these modalities is emphasized by Arroliga et al, who found that the majority of ICU patients receive sedation and many also receive neuromuscular blockers. However, there is a lack of objective evidence as to the indications for, effectiveness of, and safety of this treatment. Furthermore, it is necessary to determine whether these sedative, analgesic, and muscle relaxant regimens have negative effects on patient outcome. This is a vital objective, as it is important to ascertain whether modifying these regimens can in any way improve the poor outcomes observed in patients receiving sedation, analgesia, and neuromuscular relaxation. Consequently, there is much more work still to be done to facilitate the safe and effective sedation of critically ill patients.

Charles Weissman, MD
Jerusalem, Israel

Dr. Weissman is Professor and Chair, Department of Anesthesiology and Critical Care Medicine, Hebrew University, Hadassah School of Medicine and Hadassah-Hebrew University Medical Center. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml). Correspondence to: Charles Weissman, MD, Department of Anesthesiology and Critical Care Medicine, Hadassah-University Hospital, Kieryat Hadassah, PO Box 12000, Jerusalem, Israel 91120; e-mail: Charles@hadassah.org.il

References
Temporal Changes in Clinical Outcomes With ARDS

Acute lung injury (ALI) and ARDS are common and lethal conditions. The spectrum of lung injury represented by ALI/ARDS affects approximately 150,000 people each year in the United States, although the number may be much higher. The mortality rate associated with ALI/ARDS depends on the underlying cause, varying from < 20% for traumatically injured patients to > 60% for sepsis-induced ALI/ARDS. Crude estimates of the health-care costs associated with ALI/ARDS may exceed $5 billion per year in the United States alone. Substantial efforts have been devoted to finding effective therapies and improving clinical outcomes, and to date we have had limited, if any, success.

In this issue of CHEST (see page 525), Stapleton and colleagues provide an expanded report on ALI/ARDS patients at the University of Washington. From these subjects, they report that the fatality rates of patients with ALI/ARDS have declined over time, with sepsis-related complications being the most common cause of death at nearly 50% and respiratory failure being a relatively uncommon cause of death at < 20%. Importantly, the reductions in patient fatalities are most apparent in patients with trauma-related ALI/ARDS, while patients with sepsis-related lung injury continue to experience the highest fatality rates. The proportion of deaths that occur within the first 3 days after contracting ALI/ARDS compared to those occurring later has not changed, yet it appears that death may be occurring more swiftly for the growing percentage of patients who have life support measures withdrawn.

How does this fit with our current understanding of ALI/ARDS? While much of the data regarding outcomes in ALI/ARDS is from the same productive group of investigators, we have good evidence that patient fatality rates have been declining over the past 20 years. Early mortality with ALI/ARDS is primarily related to the inciting event, while mortality after the first 3 days often relates to an intervening complication, such as sepsis.

Interestingly, prior studies examining changes in fatalities have found that improvements were most apparent in the younger population and in those patients with sepsis, compared to the current study in which the outcomes of patients with sepsis-related ALI/ARDS have not significantly changed. Another timely finding of this study is the observation that ALI/ARDS patients are increasingly more likely to have care withdrawn prior to death, which is a finding that is consistent with data gathered in other critically ill populations where the withdrawal of life support may precede up to 90% of ICU deaths.