Sedation in the Intensive Care Unit: A Call for Evidence

Sedation in the intensive care unit (ICU), long considered a necessary but relatively benign adjunct to patient management, is now recognized as an important determinant of patient morbidity. The implementation of nurse-driven sedation protocols that minimize continuous sedative infusions, and daily interruption of infusions to allow patient awakening, have been shown to reduce the duration of mechanical ventilation and ICU stay.[1–3] Two sedatives have been associated with mortality: etomidate, because of its inhibitory effect on adrenal function, and propofol, because of its association with cardiac failure and rhabdomyolysis ("propofol infusion syndrome"). In addition, recent evidence suggests that specific sedative agents are associated with the transition to delirium in the ICU,[4] which in turn is associated with both increased morbidity and mortality.[5,6] However, considerable gaps remain in our knowledge of how to sedate critically ill patients, both in terms of specific agents and depth of sedation.

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In this issue of RESPIRATORY CARE, Siobal et al[7] present a potential solution to a difficult ICU sedation problem: that of the agitated patient who is seemingly ready for liberation from mechanical ventilation. Because agitation can be due to many causes, including delirium, pain, and dyspnea, it is often difficult to determine whether agitated patients are truly "failing" trials of spontaneous ventilation, or rather have agitation that is independent of their capacity to breathe unassisted. This problem is compounded by the fact that the administration of commonly used treatments for agitation (benzodiazepines, propofol, and opioids) may result in respiratory depression and further cloud assessment of the patient's respiratory status.

Siobal et al approached this dilemma by administering a unique sedative agent, dexmedetomidine, to 5 surgical ICU patients who had previously "failed" attempts at liberation from ventilation because of agitation. Four patients had suffered traumatic injury, including three with brain injury, and had been mechanically ventilated for between approximately 4.5 and 20 days. Dexmedetomidine infusion was initiated without a loading dose, and other sedatives, including propofol, lorazepam, and midazolam, were reduced or discontinued. Interestingly, dexmedetomidine was titrated to heart rate and blood pressure response rather than to level of consciousness. All patients were extubated within 2 hours of initiation of dexmedetomidine infusion, although one was subsequently reintubated because of upper-airway obstruction. No important adverse events were noted, although one patient exhibited transient bradycardia.

There are several reasons why dexmedetomidine might facilitate liberation from mechanical ventilation. Dexmedetomidine is an alpha-2 adrenergic receptor agonist, with resulting sympatholytic and analgesic properties[8–10] but no respiratory depressant effect.[11,12] In addition, dexmedetomidine induces sedation through normal sleep pathways, in contrast to benzodiazepines, which affect receptors at multiple sites.[13] This latter property may lead to a better quality of sedation, with the effect of reducing sedation-associated delirium.[14,15] In sum, these characteristics make dexmedetomidine an appealing agent for the transition stage from deeply sedated and mechanically ventilated to awake and spontaneously breathing, or perhaps even for routine use in the ICU.

Despite the promising results from the trial by Siobal et al and the theoretical benefits of dexmedetomidine, there are reasons to pause before advocating wider use of this agent. Previous studies of dexmedetomidine for ICU sedation were largely descriptive accounts of the quality of sedation, effects on vital signs, and pharmacokinetics and dynamics; true outcome data are lacking.[10,16–22] The study by Siobal et al is provocative but certainly limited by its small size and lack of a placebo group for comparison. If they had studied more patients, they might have found less encouraging results. In addition, given the method of administration (continuous infusion without a loading dose), there is reason to question whether dexmedetomidine had an important sedative effect at the time of initiation of spontaneous breathing trials (approximately 1 hour after beginning the infusion). Only blinded comparison to placebo can allow such an assessment. Given these issues and others, Siobal et al rightly conclude that their study merely provides justification for a large, prospective, randomized trial to determine whether dexmedetomidine does indeed facilitate liberation from mechanical ventilation.[7]

It might be argued that dexmedetomidine should be used based on its theoretical merits alone. However, nonsedative effects of dexmedetomidine may have the potential to harm patients. For example, it is not clear that the sympatholytic effect of dexmedetomidine is beneficial to crit-

ically ill patients with limited oxygen delivery or increased tissue oxygen needs. An additional issue that has not been adequately explored is the effect of dexmedetomidine on adrenal function. Dexmedetomidine is structurally related to etomidate, an imidazole that inhibits adrenal steroidogenesis. Etomidate was associated with increased mortality when administered via continuous infusion to critically ill trauma patients,[23] and there remains considerable controversy today regarding its use as an adjunct to endotracheal intubation.[24] Venn et al found that dexmedetomidine administration to post-surgical patients for 6–24 hours resulted in a blunted cortisol response to adrenocorticotrophic hormone stimulation in 5 of 10 patients after cessation of the infusion.[9] Similar "relative" adrenal insufficiency is associated with increased mortality in patients with septic shock, among others.[25] Low serum cortisol levels may also contribute to the development of post-traumatic stress disorder after recovery from critical illness.[26,27] Thus, prior to widespread application, dexmedetomidine must be studied more rigorously and for end points other than quality of sedation.

Another major reason to approach the use of dexmedetomidine with caution is cost. At my home institution, the acquisition cost for dexmedetomidine is approximately twice that for propofol, the next most-expensive agent used for sedation in the ICU. At Shands Hospital at the University of Florida, the acquisition cost for dexmedetomidine is 5 times greater than for propofol, and the administration of dexmedetomidine to 50 patients per month was projected to increase pharmacy expenditures by $850,000.[28] Thus, the use of dexmedetomidine for sedation in the ICU may substantially increase the cost of care unless acquisition cost can be offset by other benefits, such as reduced duration of mechanical ventilation, reduced length of stay, or possibly a reduced incidence of delirium. However, evidence of these benefits is currently lacking.

Unfortunately, the vast majority of the sedation literature is, with rare exception, composed of descriptive and pharmacologic, rather than outcome-oriented, studies.[29] In this era of evidence-based medicine, high-quality, prospective, randomized trials that compare sedative agents and strategies are desperately needed. Necessary end points include effects on intermediate and long-term outcomes, including duration of mechanical ventilation, length of stay, the development of delirium, the incidence of post-traumatic stress disorder, and mortality. This information is particularly important prior to the routine use of intriguing but expensive agents such as dexmedetomidine.

Steven Deem MD
Department of Anesthesiology
Harborview Medical Center
University of Washington
Seattle, Washington

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Correspondence: Steven Deem MD, Department of Anesthesiology, Harborview Medical Center, 325 Ninth Ave, Box 359724, Seattle WA 98104. E-mail: sdeem@u.washington.edu.