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A New Era for Sedation in ICU Patients

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Critically ill patients frequently require invasive monitoring and other support that can lead to anxiety, agitation, and pain. Use of sedation is essential for the comfort and safety of these patients. Options for sedation in the intensive care unit (ICU) are limited, with benzodiazepines and propofol the most common choices. In the past, these agents were generally used to keep patients motionless and to reduce memory of their experience in the ICU. However, recognition that heavy sedation may increase mortality and morbidity has led to a new model in which the emphasis is on maximizing the comfort of these patients while they remain interactive, oriented, and able to follow instructions. This new model relies on strategies such as daily interruptions of sedation, use of scores such as the Richmond Agitation-Sedation Scale to maintain target sedation level, and minimizing the use of paralytic agents.

One important consequence of lighter sedation is that physicians and critical care staff can now routinely assess the cognitive function of critically ill patients. Recent studies suggest that delirium is a common complication of being in the ICU that is often diagnosed only through active assessment by clinicians and that may be present in patients who, when observed from the foot of the bed, look calm and comfortable. Furthermore, delirium is independently associated with cognitive impairment at hospital discharge and with 6-month mortality. Unfortunately, the sedation agents, particularly benzodiazepines, are potential causes of delirium, prompting the question of whether other sedative agents may represent a better choice.

A relatively new drug, dexmedetomidine, has shown promise as a sedative agent for ICU patients and may decrease the occurrence of a combined end point of delirium or coma. Dexmedetomidine is an α₂ receptor agonist and close relative of clonidine that works via receptors distinct from the γ-aminobutyric acid receptor for benzodiazepines and propofol. As a sedative, dexmedetomidine is notable for its lack of suppression of the respiratory drive and for its potential to provide some analgesia and anxiolysis. For these reasons, this agent is potentially useful for sedation of critically ill patients. However, for the past 8 years, dexmedetomidine has been approved by the US Food and Drug Administration only for use up to 24 hours in mechanically ventilated patients, at a dose no higher than 0.7 µg/kg per hour, limiting its use for sedation of ICU patients.

In this issue of JAMA, Riker and colleagues provide data to support the idea that the development of delirium may be modifiable by choice of sedative by comparing dexmedetomidine and midazolam infusions in mechanically ventilated patients. The authors received permission to use doses of dexmedetomidine up to twice the limit approved by the Food and Drug Administration, and for up to 30 days of mechanical ventilation, with the dual goal of assessing the safety and efficacy of the extended dosing regimen. This large, double-blind, randomized controlled trial showed a decrease in the rate of delirium in critically ill patients sedated with dexmedetomidine compared with midazolam and a concomitant decrease in the time to extubation. But perhaps most important, this study, in conjunction with a recently published trial by Pandharipande et al., helps to establish dexmedetomidine as a safe alternative to benzodiazepines for long-term sedation of critically ill patients.

As evaluations of the safety of dexmedetomidine, these studies are complimentary. The trial by Pandharipande et al. involved patients from only 2 centers but was able to provide follow-up information on patients after discharge from the hospital. Pandharipande et al. found a decrease in a combined end point of days alive without delirium or coma using dexmedetomidine vs lorazepam. The trial by Riker et al. included patients from a much larger mix of ICUs in multiple countries. The trade-off in this study was more limited follow-up, likely owing to the logistical challenge of data collection in a multicenter setting. Taken together, these studies shift dexmedetomidine from a sedative suitable for the occasional patient to one useful for a majority of critically ill patients.

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A notable aspect of the design of the study by Riker et al\textsuperscript{14} was the emphasis on keeping patients “lightly” sedated throughout the study period, focusing attention on the idea that heavy sedation is not often needed, even for patients requiring mechanical ventilation for longer than 3 days. The target Richmond Agitation-Sedation Scale score ranged from −2 (light sedation) to +1 (restless) at all times. In fact, the time patients spent within this target range represented the primary outcome for the study. The authors were unable to prove their primary hypothesis, which was that patients sedated with dexmedetomidine would be in the target sedation range longer than those sedated with midazolam. But both groups were maintained in the appropriate light sedation range for an encouraging 75% of the time.

The study by Riker et al\textsuperscript{14} also illustrates a number of design challenges for trials of sedation practice. When determining the care to be used for the control population, the investigators had to find a sedative used commonly, given to patients in the same way as the study drug (such as via infusion) to allow for blinding, and dosed in a manner that allows for equivalence between the study groups—yet that still allows for flexibility in dosing according to the needs of individual patients. Other decisions involve whether to mandate certain protocols, such as daily interruption of sedation or use of weaning methods, which may be considered best practice but do not always represent common practice,\textsuperscript{13} as well as whether to allow bolus administration of the same or other medications to maintain adequate sedation, which may cloud the interpretation of results. Riker et al\textsuperscript{13} chose to initiate midazolam infusions at 0.06 mg/kg per hour (approximately 5 mg/h for their average patient—a relatively high dose), did allow open-label boluses of midazolam in both groups (which risked diluting the hypothesized benefit in the dexmedetomidine group) as well as fentanyl boluses, and included targeted sedation, with assessment at least every 4 hours. There were no mandated daily interruptions of sedation and no use of specified mechanical ventilation weaning protocols, both of which might have decreased the amount of midazolam patients received.

However, many questions remain unanswered. Because benzodiazepines have shown the greatest association with delirium,\textsuperscript{10} and guidelines recommend midazolam only for short-term use due to “unpredictable awakening and time to extubation” with longer use,\textsuperscript{7} it is perhaps not surprising that infusion of midazolam for multiple days resulted in longer time to extubation. It remains unclear whether dexmedetomidine would produce the same decrease in delirium and improvement in time to extubation if it were compared with another medication such as propofol or even inhaled anesthetic gases.\textsuperscript{16} Whether benzodiazepines given as bolus rather than infusion may have reduced delirium and length of mechanical ventilation in the midazolam group also remains an important question,\textsuperscript{17} although one difficult to assess in blinded fashion. A larger issue is whether delirium induced by medications such as midazolam is equivalent to delirium due solely to underlying critical illness.

Ultimately, the choice of sedative agent for a critically ill patient is just one of hundreds of decisions that occur during the course of care. The study by Riker et al\textsuperscript{14} is important in helping to recognize the potential implications of such decisions. With advances in technology, critical care clinicians have become increasingly skillful at stabilizing patients and supporting organ systems but now are moving beyond a focus on this short-term goal. Rather, it is important to recognize that apparently minor decisions such as the choice of sedation may have broad implications for patients.

Current evidence has linked use of sedation protocols with improvements in duration of mechanical ventilation, ICU and hospital lengths of stay, iatrogenic complications of critical illness, and tracheostomy rates.\textsuperscript{5,18,19} For patients, critical illness does not begin or end within the confines of the ICU but also can have profound implications for long-term survival,\textsuperscript{20} quality of life,\textsuperscript{21} posttraumatic stress disorder, depression, and decreases in physical function.\textsuperscript{22} Many intermediate outcomes, such as delirium, have been previously overlooked as potentially modifiable factors that may ultimately contribute to the long-term morbidities associated with critical illness.

The study by Riker et al\textsuperscript{14} failed to demonstrate that dexmedetomidine was superior to benzodiazepines for ensuring light sedation. However, the reduced prevalence of delirium is an important secondary outcome that both highlights the problems of traditional benzodiazepines and provides encouraging data regarding the potential benefits of dexmedetomidine. With the demonstration of the safety of dexmedetomidine at higher doses and for longer periods, clinicians now have a widened choice of sedatives and should always consider not only the need for sedation but also the possible clinical implications of the choice of sedative.\textsuperscript{23}

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REFERENCES