Sedative choice and ventilator-associated patient outcomes: don't sleep on delirium

Sean S. Barnes, Sapna R. Kudchadkar

Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Charlotte R. Bloomberg Children's Center, Baltimore, MD 21287, USA

Correspondence to: Sean S. Barnes, MD, MBA. Postdoctoral Fellow, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Charlotte R. Bloomberg Children's Center, 1800 Orleans Street, Suite 6318B, Baltimore, MD 21287, USA. Email: sbarne21@jhmi.edu; Sapna R. Kudchadkar, MD. Assistant Professor, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Charlotte R. Bloomberg Children's Center, 1800 Orleans Street, Suite 6318B, Baltimore, MD 21287, USA. Email: skudcha1@jhmi.edu.

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Sedation is an integral component of care for critically ill and intubated patients. The adult intensive care unit (ICU) literature suggests that the choice of sedative agent may be central to patient outcomes during and after mechanical ventilation (1). Current guidelines recommend avoidance of benzodiazepines in preference of propofol or dexmedetomidine, and highlight a preference for maintaining light levels of sedation in critically ill adult patients. These guidelines stem largely from research comparing benzodiazepine to non-benzodiazepine sedatives (2), and more specifically, dexmedetomidine to midazolam, with or without propofol (3,4). Patients who received dexmedetomidine spent less time on the ventilator and experienced less delirium. However, comparisons between dexmedetomidine and propofol are limited.

In the recent article in *Chest* entitled "Associations between different sedatives and ventilator-associated events, length-of-stay, and mortality in mechanically ventilated patients", Klompas and colleagues examine three commonly used sedatives in a "large, real world cohort" (5). The authors are to be applauded for conducting a large-scale pragmatic, retrospective cohort study to evaluate the association between use of benzodiazepines, propofol, and/or dexmedetomidine on the risk of ventilator associated events (VAEs), extubation, hospital discharge, and hospital mortality. VAEs were defined using the VAE surveillance definition algorithm (6), and classified as ventilator-associated conditions, infection related ventilator-associated complications, or the combined outcome of possible or probable pneumonia. To estimate the impact of daily sedative exposures (benzodiazepines, propofol, and dexmedetomidine) on these outcomes, the authors created proportional sub-distribution hazards models with competing risks (5). This allowed for the analysis of benzodiazepines and non-benzodiazepines (propofol and dexmedetomidine), as well as analysis between propofol and dexmedetomidine.

The investigators included in their study population all adults experiencing invasive mechanical ventilation lasting ≥3 calendar days at Brigham and Women's Hospital in Boston between 2006 and 2013. Broad inclusion criteria resulted in a large and heterogeneous study population, which the authors assert increased the study's generalizability compared to traditional randomized controlled trials examining sedative use. The large cohort studied included 9,603 consecutive episodes of mechanical ventilation and 86,714 ventilator days, with a median duration of mechanical ventilation of 6.0 days. Benzodiazepines were administered to 66% of all subjects for at least 1 day, with 62% and 12% receiving at least 1 day of propofol and dexmedetomidine, respectively. The majority of benzodiazepine use was in the form of continuous infusions (74%). Not surprisingly, sedatives were often used concurrently: all three agents were prescribed on 10% of ventilator days and two different agents were given on 46% of ventilator days. Of note, 57%

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of dexmedetomidine exposures were in cardiac surgery patients.

No association was found with time to hospital discharge or mortality when comparing all three sedatives, and benzodiazepines were associated with higher VAEs compared to regimens without exposures to benzodiazepines. In direct agent comparisons the authors found no difference, however these findings are consistent with current guidelines (1). Additionally, there is evidence to suggest that dexmedetomidine is associated with less time to extubation compared to propofol, further supporting the findings of Jakob *et al*. that patients randomized to dexmedetomidine were extubated sooner than patients randomized to propofol (4).

The limitations of the study and conclusions stem from an oversimplification of the conceptual framework and causal pathway leading to VAEs in critically ill patients. First, as the authors note, data on depth of sedation was not collected. To achieve optimal sedation management, continuous measurement of a patient's level of sedation at regular intervals is imperative; using these measures to avoid both oversedation and undersedation have the potential to reduce morbidity and mortality (7). The Pain Agitation and Delirium guidelines strongly recommend the use of a sedation scoring system to routinely assess depth of sedation and agitation in ICU patients, and the results of these sedation/agitation assessments should provide the basis for the use of sedatives in critically ill patients (1). One must temper any correlation between type of sedative and VAEs without documentation of the patients level of sedation or the patient-specific goals established by the providers. A second major limitation is that the authors fail to discuss delirium as a likely confounder on the causal pathway from benzodiazepine use to VAEs. It is possible that much of the association between benzodiazepines and VAEs is a reflection of increased delirium incidence. A recent study by Mehta and colleagues found that over 50% of mechanically ventilated adults screen positive for delirium, and that those who screen positive have a longer duration of ventilation (13 *vs*. 7 days), ICU stay (12 *vs*. 8 days), and hospital stay (24 *vs*. 15 days) (8). Benzodiazepines are a well-established pharmacologic risk factor for delirium in critically ill adults (9). Given delirium is related to both the exposure and the outcome, with increased delirium often leading to increase sedative use, it cannot be emphasized enough that delirium must be considered in any analysis of sedatives and patient outcomes.

Understanding the delicate balance between optimal sedation, sleep quality, and delirium prevention is central to improving outcomes in mechanically ventilated patients (10-12). Sleep, in all of its measurable aspects, is severely deranged in critically ill patients during mechanical ventilation, and sleep disturbance is a risk factor for delirium. Multiple patient and environmental factors in the ICU, including sedative choice, contribute to abolishing circadian rhythms and sleep-wake homeostasis (12-14). Benzodiazepines decrease restorative non-rapid eye movement sleep as well as rapid-eye movement sleep. Moreover, sleep fragmentation is known to alter patient-ventilator interaction, another possible confounder in the association between sedation choice and VAEs (13). A provider's choice of sedative can have deleterious effects on sleep, leading to a vicious cycle of increased sedation needs and ultimately delirium (10,15,16).

Recognizing these complex interactions and the importance of sleep highlights the authors' findings regarding dexmedetomidine. Unlike benzodiazepines, dexmedetomidine is known to induce a natural, sleep-like state (16). The study's results are encouraging and again support prior studies comparing dexmedetomidine and traditional sedatives. The MENDS randomized control trial by Pandharipande and colleagues found that in mechanically ventilated ICU patients (even with individualized targeted sedation management), the use of a dexmedetomidine infusion resulted in more days alive without delirium or coma and more time at the targeted level of sedation than with a benzodiazepine infusion (9). Given the growing body of evidence regarding harm associated with benzodiazepines, it is concerning to see how prevalent benzodiazepine use is in ICUs internationally. Kudchadkar *et al*. found that over 70% of intensivists' initial sedation regimen for intubated children was a combination of opioid and benzodiazepine, with midazolam being the first-line benzodiazepine 86% of the time. Interestingly, less than 1% used dexmedetomidine alone when initiating a sedation regimen (10). The adverse effects of benzodiazepine may reach further in children undergoing active neurocognitive development.

The goal of sedation management in an intensive care unit is to provide a patient with anxiolysis and comfort; however, this should not come at the expense of patient safety, restorative sleep, and delirium prevention. The authors' raised an important question regarding sedation choice and ventilator-associated outcomes, confirming the notion that benzodiazepine prescribing for sedation in critically ill patients should likely be the exception and not the norm. As we continue to investigate the optimal approaches to sedation and analgesia in critically

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ill, mechanically ventilated patients, it is crucial that pharmacology isn't considered as a silo. Downstream effects of the most commonly used sedatives, including sleep disturbances and delirium, must be prioritized in the setting of patient-specific and goal-directed sedation. This is the only path to take as we strive toward the cutting-edge of improving short and long-term outcomes for survivors of critical illness.

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Footnote

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