The evolving approach to sedation in ventilated patients: a real world perspective

Annachiara Marra[1,2], Pratik P. Pandharipande[3]

[1]Department of Medicine, Division of Allergy and Pulmonary Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA; [2]Department of Public Health, University of Naples Federico II, Napoli, Campania, Italy; [3]Department of Anesthesiology, Division of Anesthesiology Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA

Correspondence to: Pratik P. Pandharipande, MD, MSCI. Department of Anesthesiology, Medical Arts Building Suite 526, 1211 21st Avenue South, Nashville, TN 37212, USA. Email: pratik.pandharipande@vanderbilt.edu.

Provenance: This is a Guest Editorial commissioned by Section Editor Zhi Mao, MD (Department of Critical Care Medicine, Chinese People's Liberation Army General Hospital, Beijing, China).

Comment on: Klompas M, Li L, Szumita P, *et al*. Associations between different sedatives and ventilator-associated events, length of stay, and mortality in patients who were mechanically ventilated. Chest 2016;149:1373-9.

Submitted Oct 10, 2016. Accepted for publication Oct 16, 2016.
doi: 10.21037/atm.2016.12.56
View this article at: http://dx.doi.org/10.21037/atm.2016.12.56

The choice of the right sedative regimen is one of the most important supportive therapies in the treatment of critically ill patients, given mounting evidence that sedation, especially when deep, is associated with worse outcomes including mortality (1-5). The new 2013 Pain Agitation and Delirium (PAD) guidelines from the Society of Critical Care Medicine therefore has specific recommendations with regards to use of sedation in the critically ill—(I) monitor patients for level of sedation; (II) consider an analgesia first approach; (III) if a sedative is required, then a non-benzodiazepine regimen (so propofol or dexmedetomidine) should be used; and (IV) patients should be managed with the lightest level of sedation and undergo daily spontaneous awakening trial (6). These recommendations have been made on the back on numerous important investigations in this last decade, which have brought to light the perils associated with sedation, but have also provided some insights on what best practices should be (2,3,5,7-12). The specific recommendations with regards to non-benzodiazepines choice of sedative medication have been appropriately based on robust randomized controlled trials of benzodiazepines versus either propofol (11) or dexmedetomidine (7,9,12) to determine causal associations, yet the outcomes of these sedatives needed to be studied when the population sample is generalized (without the exclusions enforced in randomized controlled trials) and in real world practices where numerous confounders exist and medications are often co-administered.

Klompas *et al*. in the "Associations between different sedatives and ventilator-associated events, length of stay, and mortality in mechanically ventilated patients", published in *Chest* (13), tried to answer whether there are important differences between the most commonly used sedative regimens when used as part of usual care in the intensive care unit (ICU). The author used proportional hazard models, accounting for measures of severity of illness, likelihood of sedative choice and confounders of hospital course, to compared patients who received at least one day of propofol, dexmedetomidine or benzodiazepines on hazards for ventilator-associated events (VAEs), time to extubation and hospital discharge, and hospital mortality in a cohort of unselected patients. They retrospectively identified all episodes of invasive mechanical ventilation lasting ≥3 days, between July 1, 2006 and December 31, 2013 in a single center using a prospective database of ventilated patients, abstracted daily dichotomous (receiving *vs*. not receiving a particular sedative) and cumulative exposures to benzodiazepines, propofol, and dexmedetomidine for all patients using the hospital's electronic medication administration record, and determined VAEs electronically. VAEs were categorized as ventilator associated conditions, infection-related ventilator

associated complications, and pneumonias. Of 9,603 consecutive episodes of mechanical ventilation and 86,714 ventilator days during the study period, approximately 66% of patients received at least one day of benzodiazepines, 62% received at least one day of propofol, and 12% received at least one day of dexmedetomidine. Sensitivity analyses were used to further test these associations separately in patients with and without cardiac surgery and in those with greater than 1 day of a particular sedative. Regardless of how the data were analyzed patients treated with benzodiazepines and propofol had increased hazards for VAEs, but those on dexmedetomidine did not. Patient on benzodiazepines were associated with a greater hazard of staying mechanically ventilated, while patients on propofol and dexmedetomidine were not. Among recipients of propofol and dexmedetomidine, those on dexmedetomidine were associated with a lower likelihood of staying mechanically ventilated than propofol. Infection-related ventilator conditions were also higher in the benzodiazepine and propofol groups versus dexmedetomidine patients. There were no significant differences between propofol, benzodiazepines and dexmedetomidine on hazards for hospital discharge or death.

This investigation offers real world affirmation to clinicians who care for critically ill patients and who have to deal with the common and clinically challenging practice of determining appropriate sedation choices in routine practice. The results of this study are in line with previous literature showing that decreased exposure to benzodiazepines over propofol and dexmedetomidine may lead to improved patient outcomes. In a metaanalysis of randomized trials, Fraser *et al*. demonstrated that the use of non-benzodiazepine sedation in medical and surgical adult ICU MV patients was associated with 1.65-day shorter length of ICU stay and 1.9-day shorter duration of mechanical ventilation compared to patients receiving benzodiazepines for sedation (14). Carson *et al*. showed that even continuous use of propofol was superior to intermittent use of lorazepam with regards to outcomes such as time on mechanical ventilation (11). In the MENDS trial (Effect of sedation with dexmedetomidine *vs*. lorazepam on acute brain dysfunction in mechanically ventilated patients) lorazepam was associated with a higher risk of transitioning into delirium during each subsequent 24-h period (7) as compared to dexmedetomidine where the risk was lowered. Similar reduction in delirium rates and additionally duration of mechanical ventilation were seen in the SEDCOM study of dexmedetomidine versus midazolam, whereas the MIDEX study showed that dexmedetomidine was superior to benzodiazepines with regards to time on mechanical ventilation. Seymour *et al*. performed a secondary data analysis of hourly sedative dosing among patients enrolled at the largest site of the Awakening and Breathing Controlled Trial confirming that greater use of benzodiazepines and propofol, in ICU, was associated with adverse outcomes among mechanically ventilated patients. Benzodiazepine dose during the day, and increases at night, were associated with delayed liberation from mechanical ventilation and subsequent delirium (15). Recent advances in critical care medicine have identified acute brain dysfunction (delirium and coma) as a highly prevalent manifestation of organ failure in critically ill patients that is associated with increased length of MV, longer ICU stays, increased cost, long term cognitive impairment, and mortality (16-19) so interventions directed to prevent and/or reduce delirium burden have become important. While it is unclear how benzodiazepines predispose patients to delirium, these drugs may cause brain dysfunction through the activation of γ-aminobutyric acid ($GABA_A$) central nervous system receptors that alter levels of potentially deliriogenic neurotransmitters, such as dopamine, serotonin, acetylcholine, norepinephrine, and glutamate (7). Dexmedetomidine on the other hand acts at the level of the locus ceruleus, and therefore has a different neurotransmitter release profile, which mimics non-REM sleep (20). It is unclear if these mechanisms portend the beneficial effects seen with dexmedetomidine.

Klompas *et al*. (13), moreover, provide further data supporting the utilization of dexmedetomidine as a clinically useful and advantageous medication for many ICU patients and that it may offer some advantages over propofol. These data too are in line with the recent PRODEX trial of propofol versus dexmedetomidine where there were trends towards shorter duration of mechanical ventilation in the dexmedetomidine group (12).

Sedatives exert profound effects on the central nervous system but their effects on the immune system are potentially underappreciated. Klompas *et al*. (13) found that benzodiazepines and propofol both increased the likelihood of infection-related ventilator complications. Indeed, animal studies to date suggest some sedatives could have anti-inflammatory effects and may increase susceptibility to infection through direct effects on immune cells or indirect effects through neural-immune interactions. Propofol and benzodiazepines seem to induce suppression of the innate immune response perhaps via activation of $GABA_A$ receptors

on immune cells (21). The activation of $GABA_A$ receptors, by benzodiazepines, leads to cytoplasmic acidification in macrophages, resulting in impaired cytokine production, phagocytosis and bacteria killing (22). The α2 adrenoceptor agonists, such as dexmedetomidine, on the other hand, enhance macrophage phagocytosis and bacterial clearance (23,24), while exerting minimal effect on neutrophil function (25). Pandharipande *et al*. showed that septic patients treated with dexmedetomidine had shorter duration of acute brain dysfunction (delirium and coma), lower daily probability of delirium, shorter time on the ventilator, and improved 28-day survival as compared with septic patients treated with lorazepam (26). This mortality benefit, accentuated in septic patients may be due to several factors including the differences in the effects of these sedative regimens on both innate immunity and inflammation and also on the anti-apoptotic role of dexmedetomidine (26). On the basis of apparent increased susceptibility to spontaneous bacterial infection (9,21,22) and mortality related to benzodiazepines in the setting of infection (22), Nakafero investigated these effects in patients with Influenza-like illness (ILI). Exposure to benzodiazepines was associated with increased occurrence of both IL-I-related pneumonia and mortality (27). Benzodiazepine use was also associated with increased occurrence of asthma exacerbation and with increased all-cause mortality during a median follow-up of 2 years in a cohort of asthma patients (28) as well with an increased risk of pneumonia and long-term mortality in patients with a prior diagnosis of CAP (21). Further study will be necessary to clarify the role of sedatives on immune system and their safety in the context of infection especially in a population as the critically ill patients at high risk of infection.

While there seems to be mounting evidence supporting beneficial effects of dexmedetomidine and propofol over benzodiazepines, and some early signals that dexmedetomidine may be a superior agent than even propofol, we need larger studies with long-term outcomes including mortality, cognitive impairment and functional decline, given the importance of survivorship over just survival. Large ongoing investigations such as MENDS2 (dexmedetomidine versus propofol in severe sepsis; NCT01739933) and SPICE III (early goal-directed sedation; NCT01728558) will undoubtedly be the next chapters in advancing knowledge about best sedation techniques to liberate patients from mechanical ventilation and improve functional quality of life. In the interim large-scale implementation of the SCCM-PAD guidelines, the ICU Liberation campaign to focus attention on the ABCDEF bundle (www.iculiberation.org) and the eCASH concept of early comfort, analgesia and humane care are all good frameworks to help clinicians in managing sedation, when needed, in critically ill MV patients (29).

This study by Klompas (13) has some important limitations that need to be acknowledged. This was a single center retrospective analysis so some of the findings could be the results of residual confounding, local practice and perhaps unmeasured propensities for the sedative choices. Another limitation is that the authors did not report the total amount of drugs received by the patients, medication exposure was dichotomized and that the patients exposed to dexmedetomidine were few (12%) and for the most part they were cardiac surgery patients (57%). Additionally, changes in patient conditions, including severity of illness may not have been appropriately accounted for given the time-varying nature of these variables. Despite these limitations, this study does provide us with validation that the results from large randomized controlled trials of sedative agents are applicable in the real world setting and recommendation from recent guidelines appear justified.

Acknowledgements

None.

Footnote

Conflicts of Interest: Dr. Pandharipande has received a research grant from Hospira, in collaboration with the NIH; A Marra has no conflicts of interest to declare.

References

1. Tanaka LM, Azevedo LC, Park M, et al. Early sedation and clinical outcomes of mechanically ventilated patients: a prospective multicenter cohort study. Crit Care 2014;18:R156.
2. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med 2012;186:724-31.
3. Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-7.
4. Balzer F, Weiß B, Kumpf O, et al. Early deep sedation is

associated with decreased in-hospital and two-year follow-up survival. Crit Care 2015;19:197.
5. Kollef MH, Levy NT, Ahrens TS, et al. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. Chest 1998;114:541-8.
6. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.
7. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-53.
8. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008;371:126-34.
9. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489-99.
10. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 2012;308:1985-92.
11. Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. Crit Care Med 2006;34:1326-32.
12. Ahmed S, Murugan R. Dexmedetomidine use in the ICU: are we there yet? Crit Care 2013;17:320.
13. Klompas M, Li L, Szumita P, et al. Associations between different sedatives and ventilator-associated events, length of stay, and mortality in patients who were mechanically ventilated. Chest 2016;149:1373-9.
14. Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. Crit Care Med 2013;41:S30-8.
15. Seymour CW, Pandharipande PP, Koestner T, et al. Diurnal sedative changes during intensive care: impact on liberation from mechanical ventilation and delirium. Crit Care Med 2012;40:2788-96.
16. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 1996;335:1864-9.
17. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753-62.
18. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350:h2538.
19. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306-16.
20. Nelson LE, Lu J, Guo T, et al. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 2003;98:428-36.
21. Obiora E, Hubbard R, Sanders RD, et al. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. Thorax 2013;68:163-70.
22. Sanders RD, Godlee A, Fujimori T, et al. Benzodiazepine augmented γ-amino-butyric acid signaling increases mortality from pneumonia in mice. Crit Care Med 2013;41:1627-36.
23. Weatherby KE, Zwilling BS, Lafuse WP. Resistance of macrophages to Mycobacterium avium is induced by alpha2-adrenergic stimulation. Infect Immun 2003;71:22-9.
24. Miles BA, Lafuse WP, Zwilling BS. Binding of alpha-adrenergic receptors stimulates the anti-mycobacterial activity of murine peritoneal macrophages. J Neuroimmunol 1996;71:19-24.
25. Nishina K, Akamatsu H, Mikawa K, et al. The effects of clonidine and dexmedetomidine on human neutrophil functions. Anesth Analg 1999;88:452-8.
26. Pandharipande PP, Sanders RD, Girard TD, et al. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. Crit Care 2010;14:R38.
27. Nakafero G, Sanders RD, Nguyen-Van-Tam JS, et al. The association between benzodiazepines and influenza-like illness-related pneumonia and mortality: a survival analysis using UK Primary Care data. Pharmacoepidemiol Drug Saf 2016;25:1263-73.
28. Nakafero G, Sanders RD, Nguyen-Van-Tam JS, et al. Association between benzodiazepine use and exacerbations and mortality in patients with asthma: a matched case-

control and survival analysis using the United Kingdom Clinical Practice Research Datalink. Pharmacoepidemiol Drug Saf 2015;24:793-802.

29. Vincent JL, Shehabi Y, Walsh TS, et al. Comfort and patient-centred care without excessive sedation: the eCASH concept. Intensive Care Med 2016;42:962-71.

Cite this article as: Marra A, Pandharipande PP. The evolving approach to sedation in ventilated patients: a real world perspective. Ann Transl Med 2016;4(24):494. doi: 10.21037/atm.2016.12.56