Sedation in mechanically ventilated patients—time to stay awake?

Fabio Tanzillo Moreira[1], **Ary Serpa Neto**[1,2]

[1]Department of Critical Care Medicine, Hospital Israelita Albert Einstein, São Paulo, Brazil; [2]Department of Intensive Care, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Correspondence to: Ary Serpa Neto, MD, MSc, PhD. Av. Albert Einstein, 627, São Paulo, Brazil. Email: aryserpa@terra.com.br.

Abstract: On June, 2016, Klompas and colleagues published an article in the *Chest* entitled "Associations between different sedatives and ventilator-associated events, length of stay, and mortality in patients who were mechanically ventilated", which investigated the effects of different sedatives on ventilator-associated events (VAEs), length of stay, and mortality in patients who were mechanically ventilated. This study used data of over 9,603 patients in order to investigate patients over the age of 18 who underwent mechanical ventilation for more than 3 days over a 7-year period in a large academic medical center. The investigators found that propofol and dexmedetomidine were associated with less time to extubation compared with benzodiazepines, but dexmedetomidine was also associated with less time to extubation *vs.* propofol. This study raises important questions about the sedation of critically ill patients.

Keywords: Sedation; dexmedetomidine; propofol; benzodiazepines; delirium

Submitted Aug 13, 2016. Accepted for publication Aug 18, 2016.
doi: 10.21037/atm.2016.09.37
View this article at: http://dx.doi.org/10.21037/atm.2016.09.37

Critically ill patients are submitted to several interventions that can lead to distress and pain, like endotracheal intubation, mechanical ventilation, and central venous and arterial catheterization. Indeed, pain is one of the most common memories from patients admitted to intensive care unit (ICU) and can lead to agitation and its consequences, as accidental extubation, and removal of intravascular devices (1). Accordingly, one of the most used drugs for patients in the ICU are sedatives and analgesics (1).

For a long time, sedation of mechanically ventilated patients was based and guided by practices of anesthesiologists during surgical procedures. Indeed, until recently, the evidence regarding sedation in critically ill patients was scarce (2,3), and many physicians believed that the deepest sedation was the best option for patients admitted to the ICU under mechanical ventilation (4). As one of the main reasons was the fact that mechanical ventilation was delivered by machines incapable of synchronizing with the respiratory pattern and efforts of the patient. Consequently, deep sedation was necessary to adapt the patient to the mechanical ventilator (2).

Over the last decades, developments of new ventilators and drugs have dramatically changed the approach to the sedation of critically ill patients undergoing mechanical ventilation (1-3). Also, the recognition that oversedation, delirium and pain can lead to patient' distress and are associated with worse outcomes was also an important breakthrough in the field (2,3). Indeed, the publication of several studies evaluating sedation regimens in the ICU culminated with the elaboration of the first expert consensus in 1995 (5), followed by the guideline for the use of sedatives by the Society of Critical Care Medicine published in 2002 (6). Recently, this guideline was updated and several issues were addressed, like the use of sedation scales and the need of a sedation target for each patient (7).

Maintenance of lighter levels of sedation is associated with improved clinical outcomes in critically ill patients, such as shorter duration of mechanical ventilation and ICU length of stay (7). Indeed, to facilitate and to guide the level of sedation, the use of sedation scales are now encouraged. The Richmond Agitation-Sedation Scale (RASS) and Sedation-Agitation Scale (SAS) are the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients (7).

In the recent study by Klompas *et al*. (8), the investigators sought to evaluate associations between different

sedatives and patient' outcomes in a cohort of unselected mechanically ventilated patients. It is a retrospective study that included data collected prospectively from all patients submitted to mechanical ventilation for more than 3 days, and admitted to a single center in United States of America between 2006 and 2013. They created proportional sub-distribution hazard models with competing risks to estimate the impact of daily benzodiazepines, propofol and dexmedetomidine exposure on ventilator-associated events (VAEs), time to extubation, time to hospital discharge and death. All models were adjusted for severity of illness by calculating each patient's predicted probability of death at the time of initiation of mechanical ventilation.

The authors have found that both benzodiazepines and propofol were associated with increased risk of VAEs compared to regimens without these agents; there were trends towards decreased risks of VAEs with dexmedetomidine when compared directly to either benzodiazepines or propofol, although it was not statistically significant (8). Benzodiazepines were also associated with decreased chance of extubation compared to benzodiazepines-free regimens, meaning it extends duration of mechanical ventilation, whereas propofol and dexmedetomidine were both associated with an increased chance of extubation (8). In addition, dexmedetomidine was also associated with an increased chance of extubation when compared directly to propofol (8). Finally, there were no differences between sedation regimens regarding hospital discharge or mortality (8).

The conclusion of the authors is that sedatives vary in their associations with VAEs and time to extubation but not in their associations with time to hospital discharge or mortality. Both propofol and dexmedetomidine were associated with decreased time to extubation compared to benzodiazepines. Also, dexmedetomidine was associated with shorter time to extubation compared to propofol and may, therefore, be a preferable agent for selected patients.

The findings of the present study are in accordance with the current guidelines which recommends lighter sedation with non-benzodiazepines agents whenever possible (7). Indeed, it also shows that findings from randomized controlled trials (RCTs) extend to routine practice despite the greater complexity and diversity of patients and their treatments outside of RCTs (8). In fact, two recent RCTs showed that among ICU patients receiving prolonged mechanical ventilation, dexmedetomidine reduced duration of mechanical ventilation compared to midazolam and improved patients' ability to communicate pain compared with midazolam and propofol (8).

The fact that the minority of the patients admitted to the ICU have clearly indication for continuous deep sedation leads to development of new strategies and sedative drugs (1,3). With the exception of patients with severe respiratory failure, status epilepticus, intracranial hypertension and need of neuromuscular blockade, all the other patients usually can be managed with little or no sedation during the whole ICU stay (7). New drugs allow a controlled and lighter sedation, keeping the patient awake and active, capable to communicate pain and distress, and able to participate actively in his or her rehabilitation (9).

Dexmedetomidine is an anxiolytic, sedative and analgesic medication similar to clonidine. It is a selective agonist of α_2-adrenergic receptor notable for its ability to provide sedation without risk of respiratory depression (1,7). Compared to benzodiazepines and propofol, the pharmacological profile of dexmedetomidine allows effective light to moderate sedation with earlier emergence from sedation, minimal respiratory depression and absence of active metabolites and systemic accumulation after prolonged infusions (1,7). Until other sedatives increase the activity of gamma-aminobutyric acid neurons, dexmedetomidine induces sedation mainly by decreasing activity of noradrenergic neurons in the locus ceruleus (10). Indeed, one of the characteristics of the sedation with dexmedetomidine is that it mirrors natural sleep and, as such, provides less amnesia than benzodiazepines (10).

Similar to the study by Klompas *et al.* (8), several studies suggest dexmedetomidine for sedation in mechanically ventilated adults may reduce time to extubation and ICU length of stay (9,11,12). Moreover, some studies showed a significant reduction of delirium incidence with the use of dexmedetomidine (13). Since delirium is now recognized as a frequent and serious event in critically patients with critical impact even in long-term outcomes (14), its prevention is desired and should be pursued (1). Compared to lorazepam and midazolam the administration of dexmedetomidine resulted in similar proportions of time within the target range of sedation (13,15). However, patients assigned to dexmedetomidine had a reduced risk of delirium (13) and longer survival without delirium or coma (15).

Recently, the importance of long-term cognitive impairment after critical illness was also addressed (14). Indeed, survivors of critical illness frequently have a prolonged form of cognitive dysfunction, which is characterized by new or exacerbations of preexisting deficits in global cognition or executive function (14,16). A

multicenter study found that one out of four patients had cognitive impairment 12 months after critical illness that was similar in severity to that of patients with mild Alzheimer's disease, and one out of three had impairment typically associated with moderate traumatic brain injury (14). In addition, only 6% of patients had evidence of mild-to-moderate cognitive impairment before ICU admission, indicating that these profound cognitive deficits were new in the majority of patients (14). Finally, longer duration of delirium was associated with worse long-term global cognition and executive function (14). A recent meta-analysis suggested that dexmedetomidine treatment during perioperative conditions or for sedation in the ICU are associated with significantly better neurocognitive function compared to regimens not using dexmedetomidine, enlightening a new potential benefit of this drug (17).

The study by Klompas *et al.* (8) acknowledges some limitations. First of all, it is a single center study, decreasing its generalizability. Also, the dose of each drug was not assessed and patients were treated only as receiving or not the drug in each day. Finally, the most important point is that the exposure to dexmedetomidine was very low and mainly in patients after cardiac surgery. However, all these points were addressed by the authors in their Discussion.

In conclusion, the findings of the present study add more information regarding sedation in critically ill patients undergoing mechanical ventilation. According to the available evidence and taking into account the study by Klompas *et al.* (8), patients should be kept awake, and receive non-benzodiazepines sedatives whenever possible. Also, the use of dexmedetomidine could be associated with shorter duration of mechanical ventilation, less delirium during ICU stay and with a better cognitive performance after the recovery of critical illness. However, these findings must be confirmed in well powered studies.

Acknowledgements

None.

Footnote

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

Conflicts of Interest: The authors have no conflicts of interest to declare.

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.

References

1. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. N Engl J Med 2014;370:444-54.
2. Shehabi Y, Bellomo R, Mehta S, et al. Intensive care sedation: the past, present and the future. Crit Care 2013;17:322.
3. Riker RR, Fraser GL. Altering intensive care sedation paradigms to improve patient outcomes. Crit Care Clin 2009;25:527-38, viii-ix.
4. Merriman HM. The techniques used to sedate ventilated patients. A survey of methods used in 34 ICUs in Great Britain. Intensive Care Med 1981;7:217-24.
5. Shapiro BA, Warren J, Egol AB, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Society of Critical Care Medicine. Crit Care Med 1995;23:1596-600.
6. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30:119-41.
7. 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.
8. 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.
9. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;307:1151-60.
10. 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.
11. 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.
12. Chen K, Lu Z, Xin YC, et al. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill

patients. Cochrane Database Syst Rev 2015;1:CD010269.
13. 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.
14. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306-16.
15. 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.
16. Iwashyna TJ, Ely EW, Smith DM, et al. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 2010;304:1787-94.
17. Li B, Wang H, Wu H, et al. Neurocognitive dysfunction risk alleviation with the use of dexmedetomidine in perioperative conditions or as ICU sedation: a meta-analysis. Medicine (Baltimore) 2015;94:e597.

Cite this article as: Moreira FT, Serpa Neto A. Sedation in mechanically ventilated patients—time to stay awake? Ann Transl Med 2016;4(19):382. doi: 10.21037/atm.2016.09.37

