Kress *Critical Care* 2010, **14**:164
http://ccforum.com/content/14/3/164

CRITICAL CARE

COMMENTARY

The complex interplay between delirium, sepsis and sedation

John P Kress*

See related research by Pandharipande *et al.*, http://ccforum.com/content/14/2/R38

Abstract

Critically ill patients requiring mechanical ventilation frequently suffer from intensive care unit delirium, a syndrome associated with numerous poor measured outcomes. The relationship between delirium, sepsis, and sedation is complex. A discussion of the recent study ('Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an *a priori*-designed analysis of the MENDS [maximizing efficacy of targeted sedation and reducing neurological dysfunction] randomized controlled trial') by Pandharipande and colleagues is presented in this commentary.

Over the past decade, we have learned much about the problems associated with acute brain dysfunction during critical illness; currently, awareness of the ubiquitous presence of intensive care unit (ICU) delirium is growing. The paper by Pandharipande and colleagues [1] in the previous issue of *Critical Care* adds insight into this complex area. In 2004, Ely and colleagues [2] published groundbreaking work that identified ICU delirium as an event occurring in over 80% of mechanically ventilated patients; those with ICU delirium had a threefold higher independent mortality risk compared with those who never had ICU delirium. Over the last 10 years, this group of investigators has worked extensively in the development and validation of the confusion assessment method for the ICU (CAM-ICU) to detect and better understand ICU delirium. According to this tool, delirium is defined as an acute change or fluctuation in the course of mental status, plus inattention and either disorganized thinking or an altered level of consciousness [3]. The CAM-ICU tool uses the Richmond Agitation-Sedation Scale (RASS) to measure arousal [4]. Patients who are deeply unresponsive are categorized as comatose rather than delirious; that is, they respond only to physical/painful stimulation by moving but do not open their eyes (RASS score of –4) or have no response to verbal or physical stimulation (RASS score of –5). Patients who are neither delirious nor comatose are categorized as normal. Although coma and delirium are different conditions, both can be placed in a category of acute brain dysfunction.

Delirium (like acute brain dysfunction, for that matter) is not a disease but a syndrome with a wide spectrum of possible etiologies. Over the last few years, we have learned that ICU delirium does not come as a 'one size fits all' event. Rather, it appears that the longer [5] and more severe [6] the delirium is, the worse the patient outcomes are.

As reported in the previous issue of *Critical Care*, Pandharipande and colleagues [1] use data from the MENDS (maximizing efficacy of targeted sedation and reducing neurological dysfunction) trial, which compared dexmedetomidine with lorazepam for ICU sedation in a randomized double-blinded fashion [7]. Sixty-one percent of patients (61/103) in the MENDS trial were admitted with sepsis. In this important *post hoc* analysis of these septic patients, dexmedetomidine-sedated patients had more delirium/coma-free days, delirium-free days, and ventilator-free days and a lower 28-day mortality rate when compared with lorazepam-sedated patients [1]. It is important to realize that the randomization scheme for the MENDS trial was to dexmedetomidine versus lorazepam, not septic versus non-septic. Accordingly, the authors conclude (appropriately) that prospective clinical studies and further mechanistic preclinical studies are needed to confirm these preliminary observational results.

Acute brain dysfunction is common in patients with sepsis. The mechanisms by which such brain dysfunction occurs are not fully understood, but disturbances in inflammation and coagulation pathways leading to microvascular thrombosis are thought to be partly responsible. The commonplace administration of sedatives

*Correspondence: jkress@medicine.bsd.uchicago.edu
Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago, 5841 South Maryland, MC 6026, Chicago, IL 60637, USA

during mechanical ventilation of septic patients adds an additional layer of complexity to understanding acute brain dysfunction in these patients. As noted by Pandharipande and colleagues [1], there is some evidence that benzodiazepines and alpha-2 adrenoceptor agonists exert opposing effects on the immune system. So it stands to reason that dexmedetomidine may be more efficacious than lorazepam with regard to acute brain dysfunction in patients with sepsis.

As is the case in most well-designed trials, these results produce as many questions as they do answers. For example, in septic patients, how does one tease apart the impact of dexmedetomidine (compared with lorazepam) on sedation itself from the putative benefits of dexmedetomidine on immune modulation, apoptosis, and so on?

How does the timing of the CAM-ICU delirium assessment impact the findings in this study? Given the pharmacokinetic/dynamic properties of dexmedetomidine and lorazepam, whatever component of recovery from delirium or coma (or both) that is purely sedative-related is likely to occur over differing time intervals when these two drugs are compared (that is, slower recovery and longer delirium/coma with lorazepam). Since the multicenter MENDS trial did not mandate one particular sedation algorithm, it may be that lingering effects of lorazepam may have affected the CAM-ICU delirium or coma assessments (or both) more in the dexmedetomidine group.

The distinction between delirium and coma in the CAM-ICU tool is logical but arbitrary. As a person transitions from a RASS score of –3 (opens the eyes or moves in response to voice but does not make eye contact) to –4 (responds only to physical/painful stimulation by moving but does not open the eyes), the term coma, rather than delirium, is used. With regard to acute brain dysfunction, is the delirium-to-coma transition merely a continuum of progressively lesser degrees of arousal, or is there a fundamental change in the pathophysiology of the acute brain dysfunction with this transition? These questions remain unanswered at present.

The paper by Pandharipande and colleagues is an important advance in our understanding of the complex interconnections between acute brain dysfunction, sedation, and sepsis. However, we need further progress in our understanding of the complex pathophysiology of acute brain dysfunction in critically ill patients who require mechanical ventilation. This hypothesis-generating study lays important groundwork for future investigations of sepsis and sedation in this area.

Abbreviations

CAM-ICU, confusion assessment method for the intensive care unit; ICU, intensive care unit; MENDS, maximizing efficacy of targeted sedation and reducing neurological dysfunction; RASS, Richmond Agitation-Sedation Scale.

Competing interests

JPK has been the recipient of an unrestricted grant from Hospira (Lake Forest, IL, USA) and is on their speakers' bureau.

Published: 14 June 2010

References

1. Pandharipande PP, Sanders RD, Girard TD, McGrane S, Thompson JL, Shintani AK, Herr DL, Maze M, Ely EW; the MENDS investigators: **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.
2. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS: **Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit.** *JAMA* 2004, **291:**1753-1762.
3. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R: **Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU).** *JAMA* 2001, **286:**2703-2710.
4. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK: **The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients.** *Am J Respir Crit Care Med* 2002, **166:**1338-1344.
5. Ouimet S, Riker R, Bergeron N, Cossette M, Kavanagh B, Skrobik Y: **Subsyndromal delirium in the ICU: evidence for a disease spectrum.** *Intensive Care Med* 2007, **33:**1007-1013.
6. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH: **Days of delirium are associated with 1-year mortality in an older intensive care unit population.** *Am J Respir Crit Care Med* 2009, **180:**1092-1097.
7. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW: **Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial.** *JAMA* 2007, **298:**2644-2653.

doi:10.1186/cc9038
Cite this article as: Kress JP: **The complex interplay between delirium, sepsis and sedation.** *Critical Care* 2010, **14:**164.