Commentary

Tackling agitated delirium – the tip of the iceberg

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See related research by Reade *et al*., http://ccforum.com/content/13/3/R75

Abstract

Reade *et al*. studied 20 agitated intubated patients in a pilot open-label trial comparing the efficacy of dexmedetomidine versus haloperidol in facilitating extubation. While the study design had limitations, which are outlined by the authors themselves in the paper published in this issue of *Critical Care*, the study demonstrated an impressive reduction in time to extubation and length of stay. Dexmedetomidine is a promising sedative agent that acts via α_2-receptors and has been shown to decrease prevalence and duration of delirium in mechanically ventilated patients. Haloperidol is the recommended and standard drug to treat delirium, largely based on large case series and reports. Delirium is a common, underdiagnosed and serious problem in intensive care unit patients. Agitated delirious patients are at risk of immediate adverse events as well as prolonged respiratory support. All delirious patients are at risk of poor cognitive outcomes. Further research is needed into the pharmacological management of delirium, including the use of dexmedetomidine in the management of agitation and the clinical efficacy of haloperidol.

As reported in this issue of *Critical Care*, Reade and colleagues [1] have completed a pilot open-label trial comparing the efficacy of haloperidol with dexmedetomidine in the treatment of ventilated patients with agitation. This is an important contribution to the literature on delirium management despite the limitations of what is essentially a pragmatic feasibility study. Agitation leads to adverse events such as accidental extubation, removal of arterial and central lines and injury. The current delirium treatment used by the majority of intensivists worldwide is haloperidol. With agitation, clinicians often also use benzodiazepines for rapid control. This may result in continuing or starting respiratory support for oversedation. Also, benzodiazepines and physical restraints are deliriogenic. A recent Cochrane review concluded that benzodiazepines cannot be recommended for the control of this condition [2].

Dexmedetomidine is a highly selective α_2-receptor agonist that has been available in the US since 1999 as a short-term sedative in the intensive care unit (ICU). It has an affinity for the α_2-receptor that is eight times higher than that of clonidine and a half-life of 2 hours. It is clinically effective, has opiate-sparing properties and is well tolerated. It is not yet available for general use in Europe. Reade and colleagues studied 20 intubated agitated patients and demonstrated impressive decreases in time to extubation and ICU length of stay in patients on dexmedetomidine as opposed to haloperidol. There are case reports regarding the successful use of dexmedetomidine in agitated patients with withdrawal syndromes and facilitating extubation in 13 of 20 agitated patients difficult to wean [3,4]. Conversely, a retrospective assessment of 40 patients found transitioning to dexmedetomidine to be associated with increased agitation and pain. Five patients self-extubated and four of these needed emergency reintubation [5].

Delirium is common, life-threatening and largely ignored in most ICUs. In fact, the majority of patients with delirium are hypoactive, are quiet and lethargic, or present with a mixed hypo/hyperactive variant [6]. If clinicians do not use a simple tool to screen for diagnostic features of delirium, they are likely to miss it 70% of the time [7]. The incidence in a UK critical care unit is documented as two out of three mechanically ventilated patients [8]. The issue regarding the pharmacological management of delirium, agitated or otherwise, is the lack of evidence. Although haloperidol has been used on hundreds of thousands of patients since 1950 and is the drug of choice in all delirium guidelines, this is solely on the basis of case series or case reports rather than any robust clinical effectiveness trials. Regardless, most patients with delirium are untreated because it is usually undiagnosed. This is frustrating for those of us who are clear about the impact of delirium. The undeniable association between delirium and long-term cognitive impairment alone should prompt us to take notice [9]. Discharging patients so they can spend the rest of their lives in a nursing home

ICU = intensive care unit.

or struggling to remember names goes against all we are trying to achieve. While this study is small and unblinded and lacks objective endpoints, it is welcome not because it shows that dexmedetomidine is effective in the treatment of agitated delirium (although the findings suggest it may be), but because it shows that haloperidol may not be.

Delirium has bad outcomes. Hyperactive delirious patients are often violent and remain days longer on sedation and ventilated due to agitation. Dexmedetomidine is a good choice for investigation. But pure hyperactive delirium is just the tip of the iceberg; many more patients are quietly delirious. We do not know whether treating delirium will improve outcomes; the study has not been done. We do not know whether haloperidol decreases mortality as hypothesised by Milbrandt and colleagues [10] or increases mortality as retrospective cohort studies in demented patients have suggested [11]. Two other Cochrane reviews into delirium conclude that more trials are urgently needed [12,13]. Now clinicians need to decide whether to implement delirium screening as recommended and how to manage hypoactive delirium in their patients. Delirium screening resources are available on ICU delirium information websites [14].

Competing interests

The author declares that they have no competing interests.

References

1. Reade MC, O'Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R: **Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial.** *Crit Care* 2009, **13:**R75.
2. Lonergan E, Luxenberg J, Areosa Sastre A, Wyller TB: **Benzodiazepines for delirium.** *Cochrane Database Syst Rev* 2009, (1):CD006379.
3. Baddigam K, Russo P, Russo J, Tobias JD: **Dexmedetomidine in the treatment of withdrawal syndromes in cardiothoracic surgery patients.** *J Intensive Care Med* 2005, **20:**118-123.
4. Arpino PA, Kalafatas K, Thompson BT: **Feasibility of dexmedetomidine in facilitating extubation in the intensive care unit.** *J Clin Pharm Ther* 2008, **33:**25-30.
5. MacLaren R, Forrest LK, Kiser TH: **Adjunctive dexmedetomidine therapy in the ICU: a retrospective assessment of the impact on sedative and analgesic requirements, levels of sedation and analgesia and ventilatory and hemodynamic parameters.** *Pharmacotherapy* 2007, **27:**351-359.
6. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, 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.
7. Spronk PE, Riekerk B, Hofhuis J, Rommes JH: **Occurrence of delirium is severely underestimated in the ICU during daily care.** *Intensive Care Med* 2009 Apr 7. [Epub ahead of print].
8. Page VJ, Navarange S, Gama S, McAuley D: **Routine delirium monitoring in a UK critical care unit.** *Crit Care* 2009, **13:**R16.
9. Jackson J, Gordon S, Hart R, Hopkins RO, Ely EW: **The association between delirium and cognitive decline: a review of the empirical literature.** *Neuropsy Rev* 2004, **14:**87-98.
10. Milbrandt EB, Kersten A, Kong L, Weissfeld L, Clermont G, Fink M, Angus D: **Haloperidol is associated with lower hospital mortality in mechanically ventilated patients.** *Crit Care Med* 2005, **33:**226-229.
11. Wang P, Schneeweiss S, Avorn J, Fischer M, Mogun H, Solomon D, Brookhart M: **Risk of death in elderly users of conventional vs. atypical antipsychotic medications.** *N Engl J Med* 2005, **353:**2335-2341.
12. Siddiqi N, Stockdale R, Britton AM, Holmes J: **Interventions for preventing delirium in hospitalised patients.** *Cochrane Database Syst Rev* 2007, (2):CD005563.
13. Lonergan E, Britton AM, Luxenberg J: **Antipsychotics for delirium.** *Cochrane Database Syst Rev* 2007, (2):CD005594.
14. **ICU delirium – diagnosing, treating and preventing delirium in ICU patients** [http://www.icudelirium.co.uk].