Commentary

Dexmedetomidine for the treatment of hyperactive delirium refractory to haloperidol in non-intubated patients

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Delirium is reported to occur in up to 89% of patients admitted to the intensive care unit (ICU) (1), and delirium is an independent risk factor for increased costs, longer hospital stays, neuropsychological dysfunction, and mortality (2-4). As such, the effective treatment of delirium represents a way to not only improve patient safety and outcomes but also to decrease costs and increase hospital throughput. Multiple modalities, including both typical and atypical anti-psychotics, are available as off-label use to treat the symptoms of delirium. These agents do not treat the underlying condition, and data are conflicting on whether they can prevent delirium or decrease its duration (5-7). A promising therapy that can not only treat delirium symptoms but may also prevent the development of delirium is the alpha-2 agonist dexmedetomidine. Several studies have shown that dexmedetomidine, when used for sedation of patients on mechanical ventilation, can reduce the incidence and duration of delirium (8-11) and hasten extubation of patients with hyperactive delirium (12,13). There is little data, however, on its effectiveness in non-intubated patients. This represents an important patient population because the consequences of over-sedation are potentially catastrophic in the absence of a secure airway. In their current work, Carrasco *et al.* (14) show that the use of dexmedetomidine in non-intubated patients who failed treatment with haloperidol resulted in reduced time with symptoms of agitated delirium, more time at the target sedation level, and decreased overall costs of the patient stay.

In the present study, Carrasco *et al.* address the effectiveness of dexmedetomidine as a rescue agent for non-intubated patients with hyperactive delirium that failed treatment with haloperidol (14). In this non-randomized controlled trial, 132 non-intubated ICU patients with hyperactive delirium were enrolled, and all were initially treated with intravenous bolus haloperidol. Patients whose agitated delirium failed to be controlled with up to 30 mg of haloperidol (n=46, 34.8% of patients) were placed in the intervention group to receive dexmedetomidine. Patients whose symptoms improved with haloperidol therapy were continued on a haloperidol infusion. Despite failing treatment with haloperidol, patients in the dexmedetomidine group had a higher percentage of time at target sedation (92% *vs.* 59%, P=0.001), less over-sedation (0 *vs.* 11.6%, P=0.01), and shorter ICU length of stay (3.1 *vs.* 6.4, P<0.001) without increased incidence of hemodynamic side effects such as bradycardia or hypotension. Despite the higher pharmacy costs in the dexmedetomidine group, its use resulted in a savings of over $4,300 per patient. As such, these data suggest that dexmedetomidine may serve as a valuable tool for the treatment of hyperactive delirium in non-intubated patients. Furthermore, when including patients with delirium refractory to haloperidol and those in whom haloperidol administration resulted in adverse events such as oversedation, the failure rate for haloperidol in this study was 43%, demonstrating the ineffectiveness of haloperidol for the treatment of ICU delirium.

The study by Carrasco *et al.* is limited by its lack of randomization and blinding, increasing selection and observation biases. The authors minimize this as possible through transparent reporting of clinical characteristics and outcomes in the manuscript, including following the Trend

checklist (15), and they do not overstate their findings while acknowledging this limitation. Their manuscript is also limited by its inclusion of patients with hyperactive delirium only. The hypoactive motoric subtype of delirium is more common in the ICU than the hyperactive subtype, but there are no data to support pharmaceutical interventions to reduce its duration. Despite mixed results regarding effectiveness for data supporting pharmaceutical intervention for hyperactive delirium, the agitated symptomatology of the patient often mandates active therapy for the safety of the patient and staff, thus making this a reasonable patient population to study with regards to pharmaceutical interventions for ongoing delirium. Finally, this study supports the safety of dexmedetomidine in delirious patients not on mechanical ventilation but does not provide information on the effectiveness of dexmedetomidine as a first-line agent for agitated delirium prior to administration of an antipsychotic medication.

Although dexmedetomidine has been studied with regards to delirium outcomes, most studies have involved sedation of intubated patients. The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial was a randomized controlled trial comparing delirium-free days in intubated patients sedated with lorazepam or dexmedetomidine (8). Dexmedetomidine was associated with more time at the target sedation level and more delirium-free days. Additionally, Pandharipande *et al.* found that there was no difference in the cost of care between the two groups despite the higher cost of dexmedetomidine. Comparing dexmedetomidine with midazolam, the Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) study demonstrated a reduction in delirium prevalence with dexmedetomidine and a shorter time on mechanical ventilation (9). They also found significantly lower total costs with dexmedetomidine, primarily due to decreased ICU stay and reduced mechanical ventilation. Most recently, a randomized controlled trial of dexmedetomidine versus propofol for ICU sedation after cardiac surgery found a decreased incidence and reduced duration of delirium with dexmedetomidine, leading to a reduction in ICU time and cost related to delirium (11). Thus, results from multiple trials examining dexmedetomidine for sedation consistently demonstrate improved delirium outcomes and reduce cost with the use of dexmedetomidine.

Studies have also examined the effectiveness of dexmedetomidine in intubated patients for treatment of hyperactive delirium that was preventing extubation. Reade *et al.* found that dexmedetomidine shortened time to extubation and resulted in more ventilator free days compared to haloperidol (12). In a subsequent randomized controlled study [the Dexmedetomidine to Lessen Intensive Care Unit Agitation (DahLIA) trial], Reade *et al.* found that dexmedetomidine accelerated the resolution of delirium in intubated ICU patients and increased ventilator-free days compared to placebo (13).

Through multiple trials, dexmedetomidine has repeatedly proven itself valuable in the treatment of intubated patients with regards to delirium. Findings from these studies are consistent with the work of Carrasco *et al.* (14) demonstrating the effectiveness of dexmedetomidine for improving delirium outcomes and reducing cost. Importantly, Carrasco *et al.* specifically address the question of dexmedetomidine's utility in the treatment of non-intubated patients with hyperactive delirium. Despite its limitations, the trial is significant for a number a reasons. It is the first trial comparing use of dexmedetomidine versus an antipsychotic medication, haloperidol, in non-intubated patients. Furthermore, the use of dexmedetomidine in this population can achieve target sedation levels more reliably and reduce overall hospital cost and ICU length of stay without an increased incidence of side effects, including respiratory depression in patients without a secure airway. These data, and data from other studies questioning the efficacy of antipsychotics for delirium treatment, suggest that a randomized, controlled trial is warranted to evaluate the use of dexmedetomidine earlier in the treatment of delirium in non-intubated patients (as first-line therapy as opposed to after therapeutic failure of an antipsychotic medication). In the meantime, current evidence supports the use of dexmedetomidine for delirium prevention and treatment across a wide variety of ICU patients, including those not on mechanical ventilation.

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Footnote

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