Editorial

Delirium prevention: another piece of the puzzle

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Comment on: Su X, Meng ZT, Wu XH, *et al*. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 2016;388:1893-902.

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In an electronic publication released before print from *The Lancet* on August 16, 2016, Su *et al.* (1) presented the results of a randomized, double-blind, placebo-controlled trial in which a dexmedetomidine infusion markedly decreased the incidence of delirium in elderly patients admitted to the intensive care unit (ICU) after non-cardiac surgery. The data are compelling and novel, in that the dexmedetomidine infusion consisted of a low, sub-sedative dose. This two-center study, which included 700 patients, was well-powered to demonstrate the clinical effectiveness of a prophylactic dexmedetomidine infusion to reduce delirium.

Delirium is a common and morbid diagnosis that affects between 11% and 80% of ICU patients and is associated with both short- and long-term adverse outcomes (2). ICU delirium is associated with an increased risk for prolonged mechanical ventilation, and is potentially dangerous due to the risk for self-extubation or removal of vascular catheters, which may necessitate physical restraints (3). Long-term effects include an increased risk of cognitive impairment, greater 6-month mortality, and increased ICU and hospital length of stay, all of which are associated with increased health care costs (3-7).

Given the frequency of occurrence, delirium remains an underdiagnosed and undertreated complication of critical illness. Moreover, there are few potential methods for preventing delirium. First, investigators have validated several methods of diagnosing delirium in ICU patients. The Confusion Assessment Method for the ICU (CAM-ICU) has a sensitivity of 80% and specificity of 95.9%, and the Intensive Care Delirium Screening Checklist (ICDSC) has a sensitivity and specificity of 74% and 81.9%, respectively (8). The 2013 Diagnostic and Statistical Manual (DSM) of mental disorders (DSM-5) adjusted the diagnostic criteria for delirium and shifted from a "disturbance of consciousness" to a "disturbance in attention" (9), while preserving other previous criteria for delirium: "disturbance develops over a short period of time" and "disturbance in cognition."

Second, clinical guidelines on the pharmacologic treatment of delirium are conflicting (10,11). In the United States, the 2013 Society of Critical Care Medicine (SCCM) guidelines did not recommend haloperidol due to a lack of evidence that it reduces the duration of delirium in adult ICU patients (10). In contrast, in the United Kingdom, the National Institute of Health and Clinical Excellence recommended haloperidol or olanzapine for agitated patients (11). Despite these guidelines, haloperidol is commonly used in clinical practice for the treatment of agitated delirium; few studies support this practice or guide management for when haloperidol is ineffective (4,5,12). However, recent studies demonstrate that dexmedetomidine may effectively control delirium in patients who have not responded adequately to haloperidol (13,14).

Finally, pharmacologic or non-pharmacologic prevention of delirium is preferable to treatment, given the limited range of therapeutic options. Many pharmacologic strategies (e.g., dexmedetomidine, antipsychotics, melatonin, corticosteroids, statins, and gabapentin) have been investigated to prevent delirium, although the data have been inconsistent and conflicting (15). Dexmedetomidine,

a highly selective α_2 adrenoreceptor agonist, provides anxiolysis, sedation and analgesia with minimal respiratory depression and is increasingly utilized in the ICU given these characteristics (5,16). Furthermore, previous studies have noted a decreased delirium prevalence, possibly due to improvement in sleep quality, as based on polysomnography and subjective assessment (5,17). Dexmedetomidine produces a stage II, non-rapid-eye-movement, sleep-like state and in night-time infusions can preserve the day-night sleep cycle (18). In patients ≥60 years of age admitted to the ICU after cardiac surgery, dexmedetomidine (0.4 mcg/kg bolus followed by 0.2 to 0.7 mcg/kg/h) significantly reduced the incidence of delirium in comparison to propofol (25–50 mcg/kg/min for the infusion rate) (19).

Current non-pharmacologic interventions involve risk factor identification, with situation-specific modification (20,21), and implementation of evidence-based practices, when clinically appropriate, such as awakening and breathing, coordination with target-based sedation, delirium monitoring, and exercise/early mobility (ABCDE Bundle) (22).

Against this background, Su *et al.* (1) add to our current knowledge of the value of dexmedetomidine for prevention of delirium with a well-designed, randomized, placebo-controlled, double-blinded trial in which low-dose (0.1 mcg/kg/h) dexmedetomidine significantly decreased the occurrence of delirium during the first seven days after surgery. A total of 700 patients were enrolled, with 350 receiving the study drug for an average of 15 hours (from ICU admission until 08:00 on post-operative day one). Patients were assessed twice daily for the first seven days after surgery using the CAM-ICU. Postoperative delirium was diagnosed in 23% of placebo patients and 9% of dexmedetomidine patients. Notably, the delirium-sparing effect was significant only in patients receiving the infusion for 12.25 hours or longer. In addition, the low-dose infusion also improved subjective sleep quality and decreased ICU length-of-stay and the prevalence of non-delirium complications. Bradycardia and hypotension, commonly associated with dexmedetomidine infusions, were slightly (but not significantly) more frequent than in the placebo group.

Su *et al.* support earlier findings and enhance the body of knowledge on the use of dexmedetomidine in ICU patients as a means of preventing delirium. The large sample size, randomization, double-blinding and placebo-controlled design of the study are strengths not previously achieved in studies of dexmedetomidine prophylaxis of delirium. The delirium-sparing effect of a sub-sedative dose is also novel, as prior research, such as that reported by Djaiani *et al.* (19), demonstrated delirium reduction with more conventional infusion rates of 0.2–1.5 mcg/kg/h in a smaller study in cardiac surgery patients. Furthermore, the low infusion rate was associated with minimal cardiovascular side effects. Su *et al.* (1) have provided convincing evidence that dexmedetomidine has an important role in prevention of delirium in critically ill patients.

Acknowledgements

None.

Footnote

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

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