Commentary

Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery

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Delirium is a common morbidity after surgery and in patients admitted to the intensive care unit (ICU). The development of delirium is associated with increased hospital costs, prolonged hospital stays, and increased in-hospital mortality (1-3). Consequences of delirium continue to afflict patients even after hospital discharge. Patients with delirium are more likely to be readmitted to the hospital, to require institutionalization, develop cognitive dysfunction, and have decreased quality of life as compared to those that did not develop delirium (4-13). The impact that delirium has on healthcare costs and patient outcomes has led to a number of interventions to prevent it or reduce its duration, but unfortunately the high prevalence of delirium persists despite these attempts. Many studies of therapies to prevent postoperative or ICU delirium have focused on non-pharmacologic interventions, including multicomponent care pathways, geriatrics consultation, optimization of the patient's environment, enforcing appropriate sleep hygiene, and utilization of sensory aids (14-19). Even with multiple non-pharmacologic measures, however, delirium persists in the studied populations. Other treatment options, including pharmacologic therapies, are therefore needed to prevent postoperative and ICU delirium. While agents including antipsychotics, cholinesterase inhibitors, steroids, and many others have been studied to prevent delirium, these drugs have had mixed results at best, leading to a lack of strong recommendation for their use in clinical care guidelines (20).

Dexmedetomidine has emerged as an attractive option to both prevent and treat delirium. When used as the primary sedative for intubated medical and surgical ICU patients, dexmedetomidine reduced the duration of delirium when compared to benzodiazepines (21,22). Additionally, in patients undergoing cardiac surgery, dexmedetomidine has been shown to reduce the incidence of postoperative delirium when compared to propofol, leading to a reduction in ICU time and cost related to delirium (23). A recent trial in patients with hyperactive delirium that prevented weaning from mechanical ventilation found that dexmedetomidine increased ventilator-free hours and resolved delirium symptoms faster than placebo (24). Dexmedetomidine was studied as a rescue therapy for non-intubated ICU patients with hyperactive delirium whose agitated delirium failed to be controlled with intravenous haloperidol. Patients receiving dexmedetomidine had fewer treatment failures, less over-sedation, a shorter ICU length of stay, and less total costs compared to haloperidol (25).

No previous trial, however, has evaluated the use of sub-sedative dexmedetomidine to prevent delirium in an intubated and non-intubated patient population. The current study by Su *et al*. seeks to address these limitations, demonstrating that the use of low dose dexmedetomidine infusion in patients after noncardiac surgery, including

those that are not intubated, reduces the risk of delirium in the postoperative period (26).

In their study, Su *et al*. enrolled 700 patients after noncardiac surgery who were admitted to an ICU, 55% of whom required mechanical ventilation. Patients were randomized to receive either 0.1 mcg/kg/min dexmedetomidine or placebo from the time of ICU admission until 8 AM on postoperative day one. Patients who required sedation for mechanical ventilation also received either propofol or midazolam as their primary sedative. Patients were then followed throughout the remainder of their hospital stay, and delirium was assessed twice daily using the Confusion Assessment Method for the ICU for seven days. They found that the incidence of delirium in the first seven days was reduced from 23% to 9% (OR 0.35; 95% CI: 0.22–0.54) with use of low dose dexmedetomidine compared to placebo. This reduction in delirium was achieved without an increase in the incidence of excess sedation, as measured by the Richmond Agitation Sedation Scale (RASS). The use of dexmedetomidine reduced the incidence of all three motoric subtypes of delirium in both intubated and non-intubated patients. In patients that were intubated, placebo was associated with longer median time to extubation than dexmedetomidine [6.9 *vs*. 4.6 hours; hazard ratio (HR) 1.25; 95% CI: 1.02–1.53; P=0.03]. Additionally, the dexmedetomidine group had a statistically significant but clinically insignificant reduction in ICU length of stay (20.9 *vs*. 21.5 hours; HR 1.18; 95% CI: 1.02–1.37; P=0.03). There was no difference in hospital length of stay between groups, but patients receiving dexmedetomidine were more likely to be discharged from the hospital within 7 days (24% *vs*. 17%; OR 1.50; 95% CI: 1.04–2.18; P=0.03). Patients in the dexmedetomidine group also had slightly lower pain scores at rest and with movement at 3, 6, and 24 hours after surgery (all P≤0.001).

Importantly, these endpoints were achieved without an increase in sedation or hemodynamic complications associated with dexmedetomidine administration. RASS scores were similar between the two groups, and the incidences of bradycardia and hypotension were also similar. Patients in the dexmedetomidine group experienced less tachycardia (P=0.002), hypertension (P=0.002), and hypoxemia (P=0.001) than those receiving placebo. Thus, it appears that sub-sedative dose dexmedetomidine may be an effective and safe strategy to employ when considering the risk *vs*. benefit profile of agents to prevent delirium.

This is the first study to report on the efficacy of sub-sedative dose dexmedetomidine to reduce the development of delirium, both in non-intubated patients and in those requiring mechanical ventilation and sedation with γ-aminobutyric acid (GABA) receptor agonists. This study adds to the growing body of evidence that dexmedetomidine can reduce the development of delirium (21-23). Prior studies, however, compared dexmedetomidine to other sedating agents, either benzodiazepines or propofol. Thus, it was previously unknown whether dexmedetomidine had an intrinsic protective effect on delirium or whether the benefit was derived from avoiding agents that target the GABA receptor. In this study, patients in the dexmedetomidine group on mechanical ventilation received lower doses of propofol, which may have contributed to the observed outcomes in this sub-group. Taking this small caution aside, however, this study does suggest mechanisms other than avoidance of GABA agonists may contribute to dexmedetomidine's ability to lower the risk of delirium, especially in patients not requiring mechanical ventilation. While patient pain regimens were standardized and well balanced in the study, dexmedetomidine use appeared to lower pain scores, albeit by a small amount. Prior studies have demonstrated that increased postoperative pain scores were associated with an increased rate of postoperative delirium (27,28). Additionally, the current study found that patients receiving dexmedetomidine had improved sleep quality, which is similar to previous work (29,30). While quality improvement projects aimed at improving sleep have been shown to reduce delirium, other data has shown that sleep quality is not associated with transition to delirium (31-33). Finally, patients receiving dexmedetomidine had a significant reduction in hypoxemia, which in itself may increase risk of delirium (34). It is possible that dexmedetomidine can reduce the development of delirium via one of these mechanisms (or that these were coincident significant findings), but this study did not explore possible mediation between pain, sleep, or hypoxemia and dexmedetomidine on the development of delirium. Thus, the ability of dexmedetomidine to reduce delirium through these mechanisms remains unproven.

This study has strengths and limitations that deserve to be addressed. Strengths of the study include its large sample size, inclusion and analysis of non-intubated and intubated patients, use of important primary and secondary endpoints and adverse events, measurement of pain scores, and examination of the motoric subtypes of delirium. Another key strength of the study is that all study patients received non-pharmacologic interventions to reduce the risk of delirium, including frequent reorientation, cognitive

stimulation, early mobilization, sleep hygiene, and use of hearing or vision aids. Thus, while their baseline rate of delirium in the placebo group (23%) may seem low when compared to other trials of delirium interventions, this rate is consistent with other studies that utilized non-pharmacologic interventions (15). The study was limited by enrollment of patients after surgery, many of whom required consent via proxy due to medication administration and/or altered mentation. Delirium was not assessed at baseline. Although baseline delirium status may have randomized equally between groups, a significant percent of patients in each study arm were likely delirious at baseline, which would confound the study outcomes. Type of surgery was not accounted for in analyses despite data from other trials of patients admitted to the ICU after noncardiac surgery that demonstrated the effectiveness of agents to prevent delirium was associated with the type of surgery [e.g., haloperidol prophylaxis was effective after only intra-abdominal surgery (35)].

While the data presented in this article suggest that low dose dexmedetomidine may in fact reduce the development of delirium, the results must be interpreted with caution. The protective effect of sub-sedative dexmedetomidine dosing on the brain is conceptually challenging to accept and requires confirmation. Furthermore, many initially promising pharmacologic prevention and treatment options for delirium have failed with further study. In summary, dexmedetomidine has emerged as a compelling prevention and treatment agent for delirium in a wide variety of patient types, including both mechanically ventilated and non-ventilated patients. Results from this trial may not be sufficient to warrant prophylactic use of low dose dexmedetomidine for prevention of delirium in postoperative patients, but they fill an important gap in the current literature. Replication of the results in this trial in other studies will potentially lead to an increased role of sub-sedative doses of dexmedetomidine for the prevention of delirium.

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Footnote

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

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