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Literature Review

Articles That May Change Your Practice: Dexmedetomidine

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Sedation is commonly used in the intensive care unit (ICU) to reduce patient discomfort, improve tolerance with mechanical ventilation, reduce metabolic demands during respiratory and hemodynamic instability, and prevent accidental device removal. Delirium is a serious complication and has been associated with increased morbidity, prolonged hospital stay, worse functional recovery, and long-term decline in cognitive function. Moreover, recent studies showed that delirium was associated with increased short- and long-term mortality in patients admitted to ICUs. For decades, gamma-aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines) have been the standard of care for sedation in the ICU. However, evidence suggests these agents may increase the risk of delirium.

Dexmedetomidine, a highly selective alpha-2 adrenoreceptor agonist, produces sedation while maintaining a degree of arousability and has increasingly been used for sedation in ICU patients. The primary effect of activation of alpha-2 adrenoreceptors within the locus coeruleus is a reduction of noradrenaline release from nerve terminals, lowering plasma and cerebrospinal noradrenaline levels and producing central non–GABA-mediated sedation and spinal non–opioid-mediated analgesia. The sedative effect of dexmedetomidine, unlike other sedative agents, is achieved through the modulation of an endogenous sleep-promoting pathway without disruption of sleep architecture. Dexmedetomidine could also provide analgesia via receptors in the spinal cord and attenuate a stress response with minimal respiratory depression. Because of its unique mechanism of action, dexmedetomidine has been shown to overcome the limitations of the GABA-mimetic sedatives and thus reduce the incidence of delirium and improve survival. However, the use of dexmedetomidine as the sole or primary sedative agent in patients undergoing mechanical ventilation in a critical care setting has not been extensively studied. In this issue, a key review and a recently published trial regarding dexmedetomidine are summarized to provide the air and land critical care transport community with key findings to guide the use of this novel agent.

Chen K, Lu Z, Xin YC, Cai Y, Chen Y, Pan SM. Alpha–2 agonists for long–term sedation during mechanical ventilation in critically ill patients. *Cochrane Database Syst Rev*. 2015;1:CD010269.

The authors of this systematic review and meta-analysis searched the available literature to October 2014 to include all randomized and quasi-randomized controlled trials comparing dexmedetomidine with alternative sedatives for long–term sedation during mechanical ventilation in critically ill patients. The goal was to compare meaningful outcomes for this cohort of patients, including duration of mechanical ventilation, length of ICU stay, risk of delirium, adverse events, and mortality.

The authors included 7 studies with a total of 1,624 adult participants. All included studies investigated adults and compared dexmedetomidine with traditional sedatives, including propofol, midazolam, and lorazepam. Compared with traditional sedatives, dexmedetomidine reduced the geometric mean duration of mechanical ventilation by 22% (95% confidence interval [CI], 10%-33%; 4 studies, 1,120 participants) and the length of ICU stay by 14% (95% CI, 1%-24%; 5 studies, 1,223 participants). There was no evidence that dexmedetomidine decreased the risk of delirium (relative risk = 0.85; 95% CI, 0.63-1.14; 7 studies, 1,624 participants). The authors found no evidence that dexmedetomidine had an impact on mortality (relative risk = 0.99; 95% CI, 0.79-1.24; 6 studies, 1,584 participants). Although the quality of evidence was generally low, the authors determined dexmedetomidine reduces the length of ICU stay and mechanical ventilation but provides no mortality benefit or reduction in the incidence of delirium.

Since the Cochrane review, there have been no large-scale prospective studies comparing dexmedetomidine with traditional sedation for critically ill patients. This changed with a recently published large, multicenter randomized trial.

Shehabi BD, Howe R, Bellomo YM, et al. Early sedation with dexmedetomidine in critically ill patients. *N Engl J Med*. 2019; 380:2506-2517.

The authors conducted this phase 3, prospective, multicenter, multinational, open-label, randomized superiority trial of early goal-directed sedation compared with standard care known as the Sedation Practice in Intensive Care Evaluation (SPICE) III trial. The authors hypothesized that early goal-directed sedation with dexmedetomidine compared with standard care sedation would result in lower all-cause mortality at 90 days in critically ill patients who require mechanical ventilation.

The authors screened 29,502 patients in 74 ICUs across 8 countries to identify and enroll 4,000 critically ill adult patients who were mechanically ventilated for less than 12 hours in the ICU and expected to receive ventilatory support for longer than the next calendar day. Patients received either dexmedetomidine as the sole or primary sedative or received usual care (propofol, midazolam, or other sedatives). The target range of sedation scores on the Richmond Agitation and Sedation Scale was −2 to +1 (lightly sedated to restless). A total of 2,001 patients were assigned to the dexmedetomidine group and 1,999 to the standard care group. Follow-up was available in 1,948 in the study arm and 1,956 in the standard

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care group. The primary outcome was the rate of death from any cause at 90 days.

The primary outcome occurred in 566 of 1,948 (29.1%) patients in the dexmedetomidine group and in 569 of 1,956 (29.1%) patients in the usual care group (adjusted risk difference = 0.0 percentage points; 95% CI, −2.9 to 2.8). Although 66% of patients in the dexmedetomidine group of the pilot study achieved light sedation within 48 hours compared with 38% for standard sedation, patients in the dexmedetomidine group received supplemental propofol (64% of patients), midazolam (3%), or both (7%) during the first 2 days after randomization to achieve deeper sedation. Bradycardia and hypotension were more common in the dexmedetomidine group. More adverse events and serious adverse events were reported in the dexmedetomidine group than in the standard care group ($P = 0.003$), most commonly bradycardia (0.7%) and hypotension, along with prolonged sinus arrest (asystole, 0.1%).

The authors concluded that the use of dexmedetomidine as the primary or sole sedative in patients undergoing mechanical ventilation in the ICU did not result in lower 90-day mortality than standard care and was associated with more reported adverse events. Despite the large number of enrolled patients and adequate power to detect such a difference, the authors failed to show a significant reduction in all-cause mortality at 90 days between the dexmedetomidine group and the standard care group. This failure to detect a difference may not be solely caused by dexmedetomidine itself. In fact, the frequent use of sedation to achieve a Richmond Agitation and Sedation Scale deeper than −2 (ie, deeper than "light sedation") in both groups, as desired in the study protocol, may have negated any potential difference in primary or secondary outcomes because the 2 study groups were more alike than anticipated. The study design, with clinicians favoring deep sedation (ie, opting out of light sedation), was not deemed a protocol breach. Understanding these study nuances is key to interpreting the study results.

Although there is a growing body of evidence that the centrally mediated alpha-2 agonist sedative dexmedetomidine facilitates rousable sedation, reduces the duration of mechanical ventilation, and diminishes the occurrence of delirium, its use as the sole or primary sedative agent in patients undergoing mechanical ventilation remains unclear. Translating the knowledge regarding sedation from the ICU to the critical care transport setting is sometimes challenging. What may be appropriate or feasible in the ICU may not be applicable in the back of a moving transport vehicle, be it on land or in the air. The physiologic stresses a patient undergoes in transport may pose additional risk to the patient, and additional sedation may be considered to alleviate this physiologic response. However, deep sedation has potential short-term and long-term consequences, including the inability to communicate with the patient, prolonged immobility and resultant deconditioning, increased difficulties weaning and meaningful recovery, and increased risk of adverse events and death. Opiates, benzodiazepines, and neuromuscular blockade have been the mainstay to provide comfort to patients undergoing mechanical ventilation. Newer agents, such as dexmedetomidine, are continually sought to provide comfort and improve safety for these patients. Although these newer agents may offer a theoretical advantage to the more traditional agent, understanding how clinical trials are designed and results are analyzed is essential to providing improved care.

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