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Dexmedetomidine use in the ICU: Are we there yet?

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Expanded abstract

Citation

Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J; Dexmedetomidine for Long-Term Sedation Investigators: **Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials.** *JAMA* 2012, **307:**1151-1160.

Background

Long-term sedation with midazolam or propofol in intensive care units (ICUs) has serious adverse effects. Dexmedetomidine, an alpha-2 agonist available for ICU sedation, may reduce the duration of mechanical ventilation and enhance patient comfort.

Methods

Objective: The objective was to determine the efficacy of dexmedetomidine versus midazolam or propofol (preferred usual care) in maintaining sedation, reducing duration of mechanical ventilation, and improving patients' interaction with nursing care.

Design: Two phase 3 multicenter, randomized, double-blind trials were conducted.

Setting: The MIDEX (Midazolam vs. Dexmedetomidine) trial compared midazolam with dexmedetomidine in ICUs of 44 centers in nine European countries. The PRODEX (Propofol vs. Dexmedetomidine) trial compared propofol with dexmedetomidine in 31 centers in six European countries and two centers in Russia.

Subjects: The subjects were adult ICU patients who were receiving mechanical ventilation and who needed light to moderate sedation for more than 24 hours.

Intervention: After enrollment, 251 and 249 subjects were randomly assigned midazolam and dexmedetomidine, respectively, in the MIDEX trial, and 247 and 251 subjects were randomly assigned propofol and dexmedetomidine, respectively, in the PRODEX trial. Sedation with dexmedetomidine, midazolam, or propofol; daily sedation stops; and spontaneous breathing trials were employed.

Outcomes: For each trial, investigators tested whether dexmedetomidine was noninferior to control with respect to proportion of time at target sedation level (measured by Richmond Agitation Sedation Scale) and superior to control with respect to duration of mechanical ventilation. Secondary end points were the ability of the patient to communicate pain (measured by using a visual analogue scale [VAS]) and length of ICU stay. Time at target sedation was analyzed in per-protocol (midazolam, n = 233, versus dexmedetomidine, n = 227; propofol, n = 214, versus dexmedetomidine, n = 223) population.

Results

Dexmedetomidine/midazolam ratio in time at target sedation was 1.07 (95% confidence interval (CI) 0.97 to 1.18), and dexmedetomidine/propofol ratio in time at target sedation was 1.00 (95% CI 0.92 to 1.08). Median duration of mechanical ventilation appeared shorter with dexmedetomidine (123 hours, interquartile range (IQR) 67 to 337) versus midazolam (164 hours, IQR 92 to 380; $P = 0.03$) but not with dexmedetomidine (97 hours, IQR 45 to 257) versus propofol (118 hours, IQR 48 to 327; $P = 0.24$). Patient interaction (measured by using VAS) was improved with dexmedetomidine (estimated score difference versus midazolam 19.7, 95% CI 15.2 to 24.2; $P < 0.001$; and versus propofol 11.2, 95% CI 6.4 to 15.9; $P < 0.001$). Lengths of ICU and hospital stays and mortality rates were similar. Dexmedetomidine versus midazolam patients had more hypotension (51/247 [20.6%] versus 29/250 [11.6%]; $P = 0.007$) and bradycardia (35/247 [14.2%] versus 13/250 [5.2%]; $P < 0.001$).

Conclusions

Among ICU patients receiving prolonged mechanical ventilation, dexmedetomidine was not inferior to midazolam and propofol in maintaining light to moderate sedation. Dexmedetomidine reduced duration of mechanical ventilation compared with midazolam and improved the ability of patients to communicate pain compared with midazolam and propofol. Greater numbers of adverse effects were associated with dexmedetomidine.

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Commentary

Sedation is commonly used in the intensive care unit (ICU) to reduce patient discomfort, improve tolerance with mechanical ventilation, prevent accidental device removal, and reduce metabolic demands during respiratory and hemodynamic instability [1,2]. Continuous and deep sedation have been associated with increased risk of delirium, longer duration of mechanical ventilation, increased length of ICU and hospital stays, and long-term risk of neurocognitive impairment, post-traumatic stress disorder, and mortality [3-7]. Sedation interruption and protocolized sedation have been associated with decreased length of ICU stay and reduced duration of mechanical ventilation [4,5]. Whether combining sedation interruption and protocolized sedation improves outcome is controversial. Whereas some studies show a benefit [6], others show no difference [8].

Commonly used first-line sedative medications, including propofol and midazolam, and less commonly used medications, such as lorazepam, have many side effects. There exists wide intra- and inter-individual variability [9], resulting in unpredictable drug accumulation with benzodiazepines [10]. Lorazepam is associated with propylene glycol-related acidosis and nephrotoxicity. Propofol causes hypertriglyceridemia, pancreatitis, and propofol-related infusion syndrome [11,12]. Dexmedetomidine is a potent alpha-2 adrenoceptor agonist with an affinity for the alpha-2 adrenoceptor that is eight times higher than that of clonidine [13]. Prior data suggest that dexmedetomidine reduced duration of mechanical ventilation and resulted in earlier extubation [14,15]. In critically ill patients, use of dexmedetomidine has been associated with lower risk of delirium and coma compared with propofol, lorazepam, and midzolam [15,16]. However, safety and efficacy of prolonged dexmedetomidine infusion in the ICU have not been evaluated.

The PRODEX (Propofol vs. Dexmedetomidine) and MIDEX (Midazolam vs. Dexmedetomidine) trials attempted to answer this question with higher doses of dexmedetomidine for longer duration when compared with propofol and midazolam in mechanically ventilated patients. Both studies provide important clinical evidence that dexmedetomidine is an effective sedative agent compared with propofol and midazolam. Use of dexmedetomidine is associated with easier communication with patients, better assessment of pain (from the perspective of the caregiver), reduced delirium, and decreased time to extubation as compared with propofol. However, this finding did not translate into reduction of length of ICU or hospital stay. Among the strengths of the study are that it was a well-conducted, large, multicenter, double-blind, randomized controlled study. The trial employed frequent sedation assessment, daily sedation stops, and a double-dummy design to reduce the risk of bias.

Several important limitations to the study deserve further consideration. The weaning from mechanical ventilation and criteria for extubation were not standardized. Spontaneous breathing trials were performed in only about half of the sedation stops, as compared with approximately 60% of those screened in the Awakening and Breathing Controlled trial [6]. Whereas the incidence of neurocognitive disorders, including delirium, anxiety, and agitation, was evaluated throughout the study, the long-term neurocognitive and functional outcomes with dexmedetomidine have not been examined. Sedation was assessed from the caregivers' perspective only, and future studies should include the patients' perspective of quality of sedation. Also, this study included only patients with light to moderate sedation; thus, these findings may not be applicable to patients requiring deep sedation. In the first 24 hours of the PRODEX trial, discontinuation of dexmedetomidine was more frequent because of a lack of efficacy. As acknowledged by the authors of the PRODEX and MIDEX trials, most clinicians and centers do not consider dexmedetomidine an equivalent alternative to propofol and midazolam for long-term sedation. These trials, nevertheless, reassure clinicians regarding the safety of dexmedetomidine in terms of higher doses over a long period of time.

Recent guidelines of the Society of Critical Care Medicine recommend using non-benzodiazepine agents, such as propofol or dexmedetomidine, over benzodiazepines as a first-line sedative agent, and dexmedetomidine in patients at risk for delirium that is not related to alcohol and benzodiazepine use [11]. The opioid-sparing [11] effect of dexmedetomidine may reduce opioid requirements in critically ill patients. The most common side effects of dexmedetomidine are hypotension and bradycardia, and this limits its use in patients who are dependent on their cardiac output, such as patients in the acute phase of shock.

Recommendation

In carefully selected critically ill patients receiving prolonged mechanical ventilation, dexmedetomidine is safe and may be preferred as an alternative non-benzodiazepine agent to maintain light to moderate sedation. However, long-term outcomes, including neurocognitive effects, and the safety of dexmedetomidine are unknown.

Abbreviations

ICU, intensive care unit; MIDEX, Midazolam vs. Dexmedetomidine; PRODEX, Propofol vs. Dexmedetomidine.

Competing interests

The authors declare that they have no competing interests.

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