

Sedation with dexmedetomidine in the intensive care setting

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Abstract: Dexmedetomidine is an α -2 agonist that produces sedation and analgesia without compromising the respiratory drive. Use of dexmedetomidine as a sedative in the critically ill is associated with fewer opioid requirements compared with propofol and a similar time at goal sedation compared with benzodiazepines. Dexmedetomidine may produce negative hemodynamic effects including lower mean heart rates and potentially more bradycardia than other sedatives used in the critically ill. Recent studies have demonstrated that dexmedetomidine is safe at higher dosages, but more studies are needed to determine whether the efficacy of dexmedetomidine is dose dependent. In addition, further research is required to define dexmedetomidine's role in the care of delirious critically ill patients, as many, but not all, studies have indicated favorable outcomes.

Keywords: dexmedetomidine, sedation, critical care

Introduction

Patients in the intensive care unit (ICU) setting require invasive monitoring and treatments that often lead to anxiety and pain.¹⁻³ In particular, use of mechanical ventilation may create a variety of physical and psychological stresses.^{1,2} The use of intravenous sedatives is considered integral in the care of ICU patients, especially those who are mechanically ventilated.¹⁻⁶ Sedation is a dynamic process and varies according to the changing clinical course of the individual patient and their treatment needs.⁷ Sedation should be monitored regularly with a validated sedation scale (eg, Sedation Agitation Score, Richmond Agitation Sedation Scale [RASS], or Motor Agitation Sedation Scale) and therapy adjusted to a goal target.^{3,7,8}

Because sedation is a dynamic process, it is often a balancing act to avoid suboptimal sedation and oversedation. Suboptimal sedation can place the patient at risk for physical stress such as unplanned extubations or catheter removal, and psychological stress such as anxiety.^{1,7} Oversedation increases the risks of ventilator-associated pneumonia, increased length of ICU stay, and psychological sequelae.⁷ Use of sedation protocols that incorporate nursing-driven titration to goal sedation levels or the use of daily interruption of sedation has demonstrated improved outcomes including decreased duration of mechanical ventilation, incidence of ventilator-associated pneumonia, ICU, and hospital length of stays.^{3,7-9}

Unfortunately, there is not an ideal sedative for use in the critically ill. Most sedatives are associated with accumulation, respiratory depression, or negative hemodynamic effects.³ The use of continuous sedatives in mechanically ventilated patients increased from 39.7% in 2001 to 66.7% in 2007 in a study published from

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data from the Project IMPACT database.⁶ Propofol was used in 82.2% of patients, benzodiazepines in 31.1%, and dexmedetomidine in 4.0%. The use of dexmedetomidine is suspected to increase, at least in part, due to shortages of propofol, and unlike other sedatives dexmedetomidine does not cause respiratory depression.¹⁰

Review of mechanism of action and pharmacokinetics

Unlike most sedatives used in the ICU, dexmedetomidine is an α -2 agonist and does not work on the gamma-amino butyric acid (GABA)-mimetic system.^{10,11} Therefore, dexmedetomidine causes sedation and analgesia without depressing the respiratory drive.^{10,11} The sedative properties of dexmedetomidine are produced by the stimulation of α -2 receptors on presynaptic neurons.¹⁰ This eventually leads to a decreased release of norepinephrine from the presynaptic neuron and attenuates central nervous excitation, especially in the locus coeruleus.^{10,12–14} Dexmedetomidine has been reported to have an eight times higher affinity for the α -2 receptor than clonidine.^{11,15}

The sedation produced by dexmedetomidine has been termed “cooperative sedation”, as it allows the patient to interact with healthcare professionals.^{16,17} Cooperative sedation allows patients to be easily transitioned from sleep to wakefulness, which may aid in evaluation of neurological status and allow the patient to perform tasks.^{16–18} Although “cooperative sedation” may be achieved if other sedatives are properly dosed, dexmedetomidine maintains this throughout its usual dosage. In addition, this characteristic helps to explain why dexmedetomidine is also used for sedation of patients undergoing invasive procedure of radiological tests.¹⁰

As expected with an α -2 agonist, the most common adverse effects in a phase II study comparing dexmedetomidine with placebo in 401 patients were mainly hemodynamic abnormalities, hypotension (30%), hypertension (12%), nausea (11%), bradycardia (9%), and dry mouth (3%).^{10,11} In a meta-analysis comparing clinical trials of dexmedetomidine with placebo, propofol, or benzodiazepines in a heterogeneous population, dexmedetomidine was associated with an increased risk of bradycardia but not hypotension.¹⁹ This is similar to what has been reported in reviews of dexmedetomidine clinical trials, where bradycardia or lower mean heart rates occurred more often with dexmedetomidine than with comparators in most studies.^{10,20,21} In animals, dexmedetomidine inhibited cortisol synthesis at supratherapeutic concentrations, but this has not been reported in humans with short-term use.²⁰

Dexmedetomidine exhibits linear pharmacokinetics with a linear relationship between dose, the plasma concentration, and area under the plasma concentration-time curve.^{11,22} Following intravenous administration, dexmedetomidine is rapidly distributed and eliminated via biotransformation with very little unchanged in the urine or feces.²² It is primarily metabolized via the cytochrome (CYP) P450, predominately CYP2A6, and via direct glucuronidation to inactive metabolite, and there are no known clinically significant drug interactions.²² The elimination half-life is between 2 and 3 hours and, as expected, is prolonged in those with marked hepatic insufficiency but not renal impairment or age.¹¹

The ability of dexmedetomidine to cause both hypotension and hypertension may be explained by increasing plasma concentrations of dexmedetomidine.^{23,24} In a pharmacokinetic study in ten healthy males aged between 20 and 27 years, dexmedetomidine was dosed to reach increasing plasma concentrations.²³ The mean heart rates and plasma concentrations of norepinephrine were significantly decreased from baseline at all concentrations of dexmedetomidine. The mean arterial pressure initially decreased and was significantly lower than baseline at plasma concentrations of 0.7 ng/mL and 1.2 ng/mL. Although mean arterial pressure was not statistically different from baseline at concentrations of dexmedetomidine between 1.9 ng/dL and 5.1 ng/dL, it was significantly higher at concentrations of 8.4 ng/dL and higher. It is thought that at low plasma concentrations dexmedetomidine primary acts on the α_{2a} -receptor, which results in vasodilation. At higher concentrations, dexmedetomidine loses selectivity, working on the α_{2b} -receptor, which is associated with vasoconstriction, possibly explaining the hypertension observed predominately at high dexmedetomidine plasma concentrations.²⁴

Dosing of dexmedetomidine

Based on these opposing effects on the α_{2a} -receptor and α_{2b} -receptor, there have been controversies regarding the dosing of dexmedetomidine.^{10,20} Based on phase III clinical trials, dexmedetomidine was suggested to be administered intravenously with a 1 mcg/kg loading infusion over 10 minutes followed by a continuous intravenous infusion of 0.1–0.7 mcg/kg/hour.¹¹ One study demonstrated satisfactory sedation and hemodynamic effects when administered without a loading infusion at doses between 0.2 mcg/kg/hour and 0.4 mcg/kg/hour.²⁵ Due to the development of hypotension or bradycardia, many clinicians have decided to forego the administration of a loading infusion, and only 33% of patients received a loading infusion in a retrospective

study of dexmedetomidine in an ICU at ten institutions.²⁶ In a recent phase IV study in 375 patients, loading infusions were optional and were administered in 8.2% of those on dexmedetomidine.²⁷

Like the use of loading infusions, the maximum dose of dexmedetomidine has also been controversial.^{10,20} The phase III studies of dexmedetomidine utilized a maximum dose of 0.7 mcg/kg/hour and were conducted in surgical patients.¹¹ In a phase II study in medical patients, after the first four patients all required rescue propofol, the maximum dose was increased to 2.5 mcg/kg/hour.²⁸ More recently, in comparative trials with benzodiazepines or propofol, dexmedetomidine was dosed to a maximum dose of 1.4–1.5 mcg/kg/hour.^{20,27,29,30} In a retrospective analysis comparing patients who received up to 0.7 mcg/kg/hour with those who received greater than 0.7 mcg/kg/hour, there was not an increase in adverse effects with higher doses.³¹

Review of clinical trials: efficacy, safety, and tolerability

In the time since dexmedetomidine has been available for use as an ICU sedative, there have been many controversies.^{10,20} Initially, dexmedetomidine was studied only in postoperative ICU patients for short-term use (<24 hours) and generally with maximum doses of 0.7 mcg/kg/hour or less. The first phase II study in medical ICU patients required a protocol amendment to increase the maximum dosage to 2.5 mcg/kg/hour when the first four patients were not sedated at the maximum dosage of 0.7 mcg/kg/hour.^{10,28} This led to more controversy because these patients were not sedated at dosages suggested in the product labeling. It was not until 2007 that a prospective comparative study was published that included mostly medical patients and that demonstrated safety and efficacy with maximum dosages of 1.5 mcg/kg/hour.³⁰ Likewise, the results of a recently published meta-analysis have been controversial.¹⁹ The authors analyzed all results together, even though there are vast differences in either measurement of study endpoints or the definition of endpoints. The meta-analysis has been criticized for heterogeneity, in particular the many different ways the comparative studies measured delirium (Table 1).^{19,32}

Dexmedetomidine has been available for use as a sedative in ICU patients since 1999, based on a placebo-controlled trial of 119 cardiac and general surgery patients.³³ Of these, 14 were recruited into an open-label study of dexmedetomidine and 105 in the double-blind randomized trial. Sixty-six patients received dexmedetomidine as a loading infusion of 1 mcg/kg over 10 minutes, followed by a maintenance

infusion of 0.2–0.7 mcg/kg/hour. All patients received morphine intravenously administered in 2 mg increments for pain as needed. Intubated patients were maintained at a goal Ramsay Sedation Score of 2 or greater, and if the study drug was not adequate, a midazolam 0.02 mg/kg bolus could be administered. If more than three boluses were administered within 1 hour, a midazolam infusion could be initiated at 0.01–0.02 mcg/kg/hour. The patients in the dexmedetomidine group required significantly less midazolam than placebo (mean 4.9 ± 5.9 mcg/kg/hour versus 23.7 ± 27.5 mcg/kg/hour, $P < 0.0001$) and morphine (mean 11.2 ± 13.4 mcg/kg/hour versus 21.5 ± 19.4 mcg/kg/hour, $P = 0.0006$). There was no difference in the duration of intubation (11.4 ± 4.9 hours in the dexmedetomidine group versus 10.8 ± 5.8 hours). Significant hypotension, defined as mean arterial pressure less than 60 mmHg or more than a 30% drop or bradycardia occurred in 18 patients (27%) who received dexmedetomidine, with most events occurring during the loading infusion (eleven patients).

Similar to the placebo-controlled trial, the early comparative studies with dexmedetomidine were carried out in surgery patients.¹⁰ Venn and Grounds³⁴ compared dexmedetomidine with propofol in 40 abdominal or pelvic surgery patients (Table 1). Upon admission to the ICU, patients were randomized to dexmedetomidine or placebo. All patients received alfentanil for analgesia. Those receiving dexmedetomidine required significantly less alfentanil (median 0.8 [intraquartile range 0.65–1.2] mg/hour versus 2.5 [2.2–2.9] mg/hour, $P = 0.004$) but had similar levels of sedation (median Ramsay Sedation Score 5 [4–5] for the dexmedetomidine group versus 5 [4–6] for the propofol group, $P = 0.68$) and mean time to extubation (29 [15–50] minutes for the dexmedetomidine group versus 28 [20–50] minutes for the propofol group, $P = 0.68$). There were no differences in mean arterial pressure between groups, but those receiving dexmedetomidine had significantly lower heart rates (mean 75 ± 6 beats per minute with dexmedetomidine versus 90 ± 4 beats per minute with propofol, $P = 0.034$).

The result of the previously mentioned study are similar to those of a multicenter trial comparing dexmedetomidine with propofol in 295 patients undergoing coronary artery bypass graft surgery.³⁵ After sternal wound closure, those randomized to dexmedetomidine received a loading infusion of 1 mcg/kg administered over 20 minutes followed by 0.2–0.7 mcg/kg/hour to maintain a Ramsay Sedation Score of 3 or more during mechanical ventilation and 2 or more after extubation. Those in the propofol group received it according to each site's standard practice with the same sedation goals.

Table 1 Comparative studies with dexmedetomidine^{10,20}

Reference	Comparators	Primary endpoint	Delirium endpoint	Safety endpoint
Venn and Grounds ³⁴ Abdominal or pelvic surgery	DEX: LD 0.4 mcg/kg MD 0.2–2.5 mcg/kg/hour n = 20 Propofol: LD 1 mcg/kg MD 1–3 mcg/kg/hour n = 20	Median (IQR) alfentanil requirements 0.8 (0.65–1.2) mg/hour 2.5 (2.2–2.9) mg/hour	NR	Mean HR 75 ± 6 bpm 90 ± 4 bpm, P = 0.034
Herr et al ³⁵ CABG surgery	DEX: LD 1 mcg/kg over 20 minutes, MD 0.2–0.7 mcg/kg/hour n = 148 Propofol: investigators' standard practice n = 147	Mean Ramsay Sedation Score 4.5 4.7 P = 0.259	NR	Hypotension/hypertension 24%/12% 16%/4% P = 0.11/P = 0.018
Elbaradie et al ³⁶ Abdominal, pelvic, or thoracic Surgery	DEX: LD 2.5 mcg/kg over 10 minutes, MD 0.2–0.5 mcg/kg/hour n = 30 Propofol: LD 1 mg/kg, MD 0.5–1 mcg/kg/hour n = 30	Mean Ramsay Sedation Score 4.1 ± 1 4 ± 0.9, P = 0.50	NR	Mean HR was significantly lower in the DEX group (but only reported in a figure) P = 0.041
Corbett et al ³⁷ CABG surgery	DEX: LD 1 mcg/kg over 10 minutes, MD 0.2–0.7 mcg/kg/hour n = 43 Propofol: 5–75 mcg/kg/minute n = 46	Patient comfort using a 1–10 point Hewitt questionnaire Median comfort level 4.5 3.5, P = 0.24	Assessment NR 2.3% 2.2%, P > 0.99	Hypotension (SBP < 90 mmHg or MAP 60 mmHg) 81.4% 67.4%, P = 0.13
MENDS trial ³⁰ Medical/surgical ICU maximum length 120 hours	DEX: LD none, 0.15–1.5 mcg/kg/hour n = 52 Lorazepam: 1 mg/hour titrated to maximum 1.5 mg/hour n = 51	Days alive without delirium/coma Median 7.0 days Median 1.0 day, P = 0.01	CAM-ICU 79% 82% P = 0.65	HR < 60 bpm 17% 4% P = 0.03
Esmaglu et al ⁴¹ Eclampic patients	DEX: LD 1 mcg/kg over 20 minutes, MD 0.7 mcg/kg/hour n = 20 Midazolam: LD 0.05 mg/kg MD 0.1 mcg/kg/hour n = 20	Need for nitroglycerine/nitroprusside 45%/10% 90%/65% P = 0.006/P = 0.001	NR	Mean HR was significantly lower in the DEX group (but only reported in a figure) P < 0.05
Maldonado et al ⁴² Elective heart surgery	DEX: LD 0.4 mcg/kg, MD 0.2–0.7 mcg/kg/hour n = 40 Midazolam: 0.5–2 mg/hour, n = 40 Propofol: 25–50 mcg/kg/minute, n = 38	Delirium within 3 days of surgery (DSM-IV-TR) 3% 50% 50%, P < 0.001 for midazolam or propofol versus DEX		NR
Reade et al ⁴³ Medical/surgical ICU	DEX: LD optional, MD 0.2–0.7 mcg/kg/hour n = 10 Haloperidol: LD optional, MD 0.5–2 mg/hour n = 10	Time to extubation or tracheostomy Median 19.9 hours Median 42.5 hours P = 0.016	ICDSC (prior to/ during study) 50% 50% P > 0.99	QTc prior to/during 0.441/0.395 seconds 0.426/0.446 seconds During study P = 0.006
Ruokonen et al ²⁹ Medical/surgical ICU maximum length 14 days	DEX: LD none, MD 0.25–1.4 mcg/kg/hour n = 41 Propofol: 0.8–4 mcg/kg/hour or midazolam intermittent 1–2 mg bolus if ≥3 per hour then continuous infusion 0.04–0.2 mcg/kg/hour n = 44	Time in target RASS Median 64% Median 63% P > 0.05	CAM-ICU 43.5% 25% P = 0.035	Serious adverse events 100% 95.5% P = 0.049 DEX: 7.3 developed bradycardia

(Continued)

Table 1 (Continued)

Reference	Comparators	Primary endpoint	Delirium endpoint	Safety endpoint
SEDCOM ²⁷ Medical/surgical ICU, trauma, and burn patients excluded, maximum length 30 days	DEX: LD optional, MD 0.2–1.4 mcg/kg/hour n = 244 Midazolam: LD optional, MD 0.02–0.1 mcg/kg/hour	Time in target RASS 77.3% 75.1% P = 0.18	CAM-ICU 54% 76.6% P < 0.001	HR < 40 bpm or >30% decrease 42.2% 18.9% P < 0.001
Mirski et al ⁴⁴ Crossover study of awake intubated brain-injured (n = 18) and nonbrain-injured (n = 12) ICU patients	All patients received concurrent fentanyl DEX: LD none 0.2–0.7 mcg/kg/hour Propofol: LD none, 20–70 mcg/kg/minute	Change in cognitive function using ACE Difference between DEX and propofol 19.2% (95% CI 12.3–26.1 P < 0.001) with increased ACE score on DEX	CAM-ICU One patient	Modest bradycardia with DEX –7.7 bpm, P < 0.01

Abbreviations: ACE, Adaptive Cognitive Exam; bpm, beats per minute; CABG, coronary artery bypass graft; CAM-ICU, Confusion Assessment Method-Intensive Care Unit; CI, confidence interval; DEX, dexmedetomidine; DSM-IV-TR, Diagnostic and Statistical Manual, 4th ed, text version; HR, heart rate; ICDSC, Intensive Care Delirium Screening Checklist; ICU, intensive care unit; IQR, interquartile range; LD, loading dose; MAP, mean arterial pressure; MD, maintenance dose; NR, not reported; RASS, Richmond Agitation Sedation Scale; SBP, systolic blood pressure.

The mean sedation score (4.5 for dexmedetomidine versus 4.7 for propofol, $P = 0.259$) and median extubation time (410 minutes [310–584] for dexmedetomidine versus 462 minutes [323–808] for propofol, $P = 0.05$) were similar between groups. The mean morphine dose from sternal closure to 6 hours after extubation was significantly decreased in the dexmedetomidine group (0.23 ± 0.35 mg/hour for dexmedetomidine versus 0.84 ± 0.35 mg/hour for propofol, $P < 0.001$). There was no difference in hypotension (24% for dexmedetomidine versus 16% for propofol, $P = 0.11$) or bradycardia (3% for dexmedetomidine versus 1% for propofol, $P = 0.45$), but more hypertension occurred in the dexmedetomidine group (12% for dexmedetomidine versus 4% for propofol, $P = 0.018$), although the study did not define hypotension or hypertension.

Dexmedetomidine was also demonstrated to decrease fentanyl requirements in 60 patients after major thoracic, abdominal, or pelvic cancer surgery.³⁶ After surgery, patients were randomized to receive dexmedetomidine 0.4 mcg/kg loading infusion administered over 10 minutes followed by 0.2–0.5 mcg/kg/hour or propofol 1 mcg/kg followed by 0.5–1 mcg/kg/hour. The mean Ramsay Sedation Scale (4 ± 0.9 for dexmedetomidine versus 4.1 ± 1 for propofol, $P = 0.59$) and extubation times (30 ± 15 minutes for dexmedetomidine versus 35 ± 12 minutes for propofol, $P = 0.32$) were similar between groups. The total fentanyl dose was significantly lower in the dexmedetomidine group (15 ± 10.5 mcg for dexmedetomidine versus 75 ± 15 mcg for propofol, $P = 0.0045$). Although mean arterial pressure was not different between groups, those receiving dexmedetomidine had lower mean heart rates than the propofol group (Table 1).

Unlike the previous studies, a single-site study comparing dexmedetomidine with propofol in patients undergoing coronary artery bypass graft surgery did not find decreased opioid requirements.³⁷ Eighty-nine patients were prospectively randomized to dexmedetomidine administered as 1 mcg/kg load over 15 minutes followed by 0.2–0.7 mcg/kg/hour or propofol 5–75 mcg/kg/minute. The primary outcome was patient satisfaction using a modified Hewitt sedation questionnaire. The groups had similar satisfaction scores (median 4.5 [1.0–8.4] for the dexmedetomidine group versus 3.5 [1.5–5.0] for the propofol group, $P = 0.24$), length of mechanical ventilation (mean 10.2 ± 12.8 hours for dexmedetomidine versus 8.97 ± 7.69 for propofol, $P = 0.59$), morphine requirements (median 6 [4–8] mg for dexmedetomidine versus 6 [4–10] mg for propofol, $P = 0.32$), and midazolam requirements (median 1.5 [0.5–2.5] mg for dexmedetomidine versus 1 [0–3.0] mg for propofol, $P = 0.32$). Although the majority of patients developed hypotension, there was no difference in the incidence of hypotension between the two groups (81.4% for dexmedetomidine versus 67.4% for propofol, $P = 0.13$). Patients receiving dexmedetomidine had a significantly lower nadir heart rate (68.1 ± 10.1 beats per minute for dexmedetomidine versus 74.9 ± 11.2 for propofol, $P = 0.003$), and one patient in the dexmedetomidine experienced delirium. Based on these studies, dexmedetomidine is usually associated with a similar extubation time with fewer opioid requirements compared with propofol for short-term sedation in postoperative critically ill patients. However, many questions still remained about the role of dexmedetomidine in nonsurgical patients and use compared with benzodiazepines.^{10,20}

In 2007, the first study to address some of these issues was published. The MENDS (Maximizing Efficacy of Targeted Sedation and Reducing Neurologic Dysfunction) study compared dexmedetomidine with continuous lorazepam for up to 5 days at two institutions in 106 mechanically ventilated patients.³⁰ Approximately 70% were medical patients and 30% were surgical patients. The primary outcomes were days alive without coma or delirium and percentage of time spent at RASS target. Dexmedetomidine was administered without a loading infusion at 0.15 mcg/kg/hour to a maximum of 1.5 mcg/kg/hour and lorazepam 1–10 mg/hour. Those receiving dexmedetomidine had more days without coma or delirium (mean 7.0 days versus 3.0 days, $P = 0.01$) due to a lower prevalence of coma (63% versus 92%, $P < 0.001$) but a similar prevalence of delirium (79% versus 82%, $P = 0.65$). More time was spent within 1 point of the RASS goal in the dexmedetomidine group (80%) compared with in the lorazepam group (67%, $P = 0.04$). The median dose of dexmedetomidine was 0.74 (0.39–1.04) mcg/kg/hour and the median lorazepam dose was 3 (2.2–6) mg/hour. This study has been criticized because it compared continuous dexmedetomidine with continuous lorazepam, which has a longer half-life, instead of as needed lorazepam, and because daily interruption was not mandated in this study.^{20,38–40}

In 2009, the phase IV multicenter SEDCOM (Safety and Efficacy of Dexmedetomidine Compared to Midazolam) was published.²⁷ Critically ill surgical and medical patients requiring mechanical ventilation and sedation for more than 24 hours were randomized to dexmedetomidine administered between 0.2 mcg/kg/hour and 1.4 mcg/kg/hour with an optional loading dose of 1 mcg/kg or midazolam starting at 0.06 mcg/kg/hour with an optional loading of 0.05 mg/kg. Study drugs were titrated to an RASS score of –2 to +1. Of the 375 patients randomized, 366 (dexmedetomidine $n = 244$; midazolam $n = 122$) were included in the primary analysis, which was time in target sedation range. Approximately 85% of patients were medical, and optional loading doses were administered in 8.2% of dexmedetomidine patients and 7.4% of midazolam patients, $P = 0.84$. The mean dexmedetomidine maintenance infusion was 0.83 ± 0.37 mcg/kg/hour and 0.056 ± 0.028 mcg/kg/hour or approximately 5 ± 2.5 mg/hour for midazolam. There was no difference in the primary endpoint between the dexmedetomidine and midazolam groups (77.3% versus 75.1%, $P = 0.18$). Patients in the dexmedetomidine group had a shorter median time to extubation (1.9 days for dexmedetomidine versus 5.6 days for midazolam, $P = 0.01$), although both groups had a similar ICU length of stay (5.9 days for dexmedetomidine

versus 7.6 days for midazolam, $P = 0.24$). Bradycardia, defined as a heart rate less than 40 beats per minute or more than a 30% decrease in heart rate from baseline, was more prevalent in the dexmedetomidine group (42.2% versus 18.9%, $P < 0.001$). Similar to the criticisms of the MENDS trial, use of midazolam with its longer half-life and active metabolites, as well as the lack of required daily sedation interruptions, may have contributed to these differences.

Dexmedetomidine was compared with midazolam in a randomized study of 40 women with eclampsia.⁴¹ After pregnancy was terminated by cesarian delivery, sedation was maintained to a target Ramsay Sedation Scale of 2–3 with dexmedetomidine (loading dose 1 mcg/kg over 20 minutes, maintenance 0.7 mcg/kg/hour) or midazolam (loading dose 0.05 mg/kg followed by 0.1 mcg/kg/hour). The primary outcome was need of additional antihypertensives. Significantly fewer patients in the dexmedetomidine group required nitroglycerin (45% versus 90%, $P = 0.006$) or nitroprusside (65% versus 10%, $P = 0.001$). Although the median duration of study drug was similar (25 [5–74] hours for dexmedetomidine versus 21 [4–48] for midazolam, $P = 0.45$), the median duration of ICU stay was significantly lower in the dexmedetomidine group (45.5 [15–118] hours for dexmedetomidine versus 83 [15–312] for midazolam, $P = 0.021$).

An open-label study of 90 patients undergoing cardiac valve surgery compared dexmedetomidine with propofol or midazolam.⁴² After randomization, patients received dexmedetomidine as a load of 0.4 mcg/kg followed by an infusion of 0.2–0.7 mcg/kg/hour, midazolam infusion of 0.5–2 mg/hour, or propofol infused at 25–50 mcg/kg/minute. All study drugs were titrated to a Ramsay Sedation Score of 3 while intubated and 2 if extubated. The primary endpoint was the development of delirium measured by Diagnostic and Statistical Manual of Psychiatric Disorders criteria. The mean dosage and length of study drugs were dexmedetomidine 0.35 mcg/kg/hour for 13 hours, midazolam 1.5 mg/hour for 10 hours, and propofol 26.3 mcg/kg/minute for 11 hours. The incidence of delirium was significantly less in the dexmedetomidine group (3%) compared with midazolam (50%) or propofol (50%, $P < 0.001$ for dexmedetomidine versus midazolam and dexmedetomidine versus propofol). The mean ICU length of stay was similar between groups (dexmedetomidine 1.9 ± 0.9 days, midazolam 3 ± 3 days, propofol 3 ± 2 days), but was significantly longer in the patients who developed delirium than those who did not (4.1 versus 1.9 days, $P < 0.001$).

Dexmedetomidine was compared with haloperidol in an open-label study of 20 patients who were considered to

require mechanical ventilation only due to a high degree of agitation (RASS > 2).⁴³ Patients were randomized to receive dexmedetomidine 0.2–0.7 mcg/kg/hour or haloperidol continuous infusion 0.5–2 mg/hour to determine the time of study drug to extubation or tracheostomy. Secondary endpoints included delirium defined by the Intensive Care Delirium Screening Checklist. The median length of mechanical ventilation was significantly lower in the dexmedetomidine group (19.9 [7.3–24] hours versus 42.5 [23.2–117.8] hours, $P = 0.016$). At baseline, seven patients were delirious (three for dexmedetomidine, four for haloperidol, $P = 0.41$), and ten patients were delirious during the study (five for dexmedetomidine, five for haloperidol, $P > 0.99$). Unfortunately, there were no formal weaning protocol for mechanical ventilation, and bedside nurses were responsible for transitioning the patients to spontaneous ventilation, which may have confounded the results.²⁰

In a randomized double-blind pilot study, dexmedetomidine was compared with midazolam or propofol for sedation between 1 day and 14 days in 85 patients.²⁹ Dexmedetomidine was administered without a loading infusion to maintain a target RASS starting at 0.8 mcg/kg/hour then adjusted stepwise to 0.25 mcg/kg/hour, 0.5 mcg/kg/hour, 0.8 mcg/kg/hour, 1.1 mcg/kg/hour, or 1.4 mcg/kg/hour at unspecified time points. The median dexmedetomidine dosage was 0.8 mcg/kg/hour and the duration was 40 hours (range 3–198 hours). In the midazolam/propofol group, two-thirds received propofol. There was no difference in the median percentage of time at target sedation (dexmedetomidine 64%, midazolam/propofol 63%, $P > 0.05$), but the subset of dexmedetomidine patients with a goal of deep sedation (RASS –4 or –5, eight per group) spent significantly less time at target sedation (42% versus 62%, $P = 0.006$). Delirium was also assessed as secondary endpoint using Confusion Assessment Method-Intensive Care Unit, and unlike previous studies significantly more patients in the dexmedetomidine group were delirious (43.5% dexmedetomidine versus 25% midazolam/propofol, $P = 0.035$).

Cognitive effects were compared in a crossover study of 30 awake, intubated patients receiving dexmedetomidine-based sedation or propofol-based sedation.⁴⁴ Eighteen of the 30 patients had brain injury. In the double-blinded study after randomization, patients' baseline cognitive function was assessed by a neurological intensivist using the validated Adapted Cognitive Exam (100-point scale). Fentanyl or study drug was then titrated to achieve an RASS of 0–1 and after 30 minutes goal sedation and cognitive function were reassessed. Following a 3-hour washout period during

which fentanyl was continued, the process was repeated with the other study drug. Dexmedetomidine was administered without a loading dose starting at 0.2 mcg/kg/hour to a maximum of 0.7 mcg/kg/hour, and propofol was started at 20 mcg/kg/minute to a maximum of 70 mcg/kg/minute. The mean dexmedetomidine dosage was 0.3 ± 0.1 mcg/kg/hour and propofol was 23.8 ± 13.7 mcg/kg/minute. Sedation with dexmedetomidine improved cognition by a mean of 6.8 points (95% confidence interval [CI] 1.2 to 12.4, $P = 0.018$), and propofol decreased cognition by a mean of –12.4 points (95% CI –8.3 to 16.5, $P < 0.001$). In post hoc analysis, modest bradycardia was noted with dexmedetomidine (–7.7 beats per minute, $P < 0.01$).

Patient perspectives

Dexmedetomidine does not affect the GABA system, unlike most ICU sedatives, and it promotes the physiological sleep cycle, allowing for increased communication with caregivers.^{10,37} Theoretically, this may make for better patient satisfaction, but very few data are published. In the previously mentioned study comparing dexmedetomidine with propofol in patients undergoing coronary artery bypass graft surgery, patients receiving dexmedetomidine reported statistically more discomfort and sleep disturbances, with a trend toward more pain.³⁷ This could be due to the fact that dexmedetomidine does not cause amnesia like other sedatives, but there was no difference in this study in patients' overall awareness as a marker of amnesia. More studies are needed to determine patients' perceptions of sedation with dexmedetomidine.

Place in therapy

Although dexmedetomidine has been available for over 10 years, there have been many controversies with regard to its role in delirious patients, dosing, and neuroprotection.¹⁰ Dexmedetomidine does not produce respiratory depression and is often used in patients who are not mechanically ventilated or are actively being weaned from mechanical ventilation.^{10,26} Dexmedetomidine allows for cooperation and ease of neurological examination, although more studies are needed to determine whether dexmedetomidine is neuroprotective.^{10,20} Conversely, in at least one clinical trial, dexmedetomidine was associated with significantly less time at goal sedation when heavy sedation is needed. Therefore, the use of dexmedetomidine for deep sedation should be discouraged.²⁹ Likewise, until more data are published, dexmedetomidine is not preferred for sedation in those who are chemically paralyzed. More data are needed to

determine whether increasing the dosage of dexmedetomidine increases efficacy. In a recent retrospective analysis, those who received 0.7 mcg/kg/hour or less of dexmedetomidine had significantly more time at goal sedation levels than those receiving more than 0.7 mcg/kg/hour.³¹ Based on the results of this study, it could be concluded that those who respond well to dexmedetomidine do so at lower doses, and that increasing the dose may not improve efficacy. However, further research is necessary to fully address optimal dosing of dexmedetomidine. Although dexmedetomidine is often used in substance withdrawal, especially alcohol withdrawal, no clinical trial has been published to date.^{10,26} Studies evaluating the impact of dexmedetomidine on delirium in the ICU as secondary endpoints have produced mixed results, but a number of trials in this area are currently being conducted (NCT 00151865, NCT 001140429, NCT 00561678, NCT00455154, NCT 001378741). Finally, dexmedetomidine is associated with hemodynamic side effects such as hypotension, hypertension, and bradycardia, including cases of systole.^{20,21} Staff should be educated about its possible side effects, and caution should be used in patients with a significant decrease in baseline heart rate or significant cardiac disease.^{20,21}

Conclusion

Dexmedetomidine is an α -agonist that does not produce respiratory depression and is an option for sedation in ICU patients. However, it is associated with hemodynamic side effects, including clinically significant bradycardia. More studies are needed to define the role of dexmedetomidine, especially in the delirious patient.

Disclosure

The authors report no conflicts of interest in this work.

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