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Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients
A Randomized Trial

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P ROVIDING SEDATION FOR PA-tient comfort is an integral component of bedside care for nearly every patient in the intensive care unit (ICU). For decades, γ-aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines such as midazolam) have been the most commonly administered sedative drugs for ICU patients worldwide.[1-5] Practice guidelines for providing sedation in the ICU have identified the need for well-designed randomized trials comparing the effectiveness of different sedative agents for important clinical outcomes.[1] Despite the well-known hazards associated with prolonged use of GABA agonists,[6-12] few investigations of ICU sedation have compared these agents to other drug classes.[12-14] Instead, the recent focus in

Context γ-Aminobutyric acid receptor agonist medications are the most commonly used sedatives for intensive care unit (ICU) patients, yet preliminary evidence indicates that the α_2 agonist dexmedetomidine may have distinct advantages.

Objective To compare the efficacy and safety of prolonged sedation with dexmedetomidine vs midazolam for mechanically ventilated patients.

Design, Setting, and Patients Prospective, double-blind, randomized trial conducted in 68 centers in 5 countries between March 2005 and August 2007 among 375 medical/surgical ICU patients with expected mechanical ventilation for more than 24 hours. Sedation level and delirium were assessed using the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for the ICU.

Interventions Dexmedetomidine (0.2-1.4 μg/kg per hour [n=244]) or midazolam (0.02-0.1 mg/kg per hour [n=122]) titrated to achieve light sedation (RASS scores between −2 and +1) from enrollment until extubation or 30 days.

Main Outcome Measures Percentage of time within target RASS range. Secondary end points included prevalence and duration of delirium, use of fentanyl and open-label midazolam, and nursing assessments. Additional outcomes included duration of mechanical ventilation, ICU length of stay, and adverse events.

Results There was no difference in percentage of time within the target RASS range (77.3% for dexmedetomidine group vs 75.1% for midazolam group; difference, 2.2% [95% confidence interval {CI}, −3.2% to 7.5%]; P=.18). The prevalence of delirium during treatment was 54% (n=132/244) in dexmedetomidine-treated patients vs 76.6% (n=93/122) in midazolam-treated patients (difference, 22.6% [95% CI, 14% to 33%]; P<.001). Median time to extubation was 1.9 days shorter in dexmedetomidine-treated patients (3.7 days [95% CI, 3.1 to 4.0] vs 5.6 days [95% CI, 4.6 to 5.9]; P=.01), and ICU length of stay was similar (5.9 days [95% CI, 5.7 to 7.0] vs 7.6 days [95% CI, 6.7 to 8.6]; P=.24). Dexmedetomidine-treated patients were more likely to develop bradycardia (42.2% [103/244] vs 18.9% [23/122]; P<.001), with a nonsignificant increase in the proportion requiring treatment (4.9% [12/244] vs 0.8% [1/122]; P=.07), but had a lower likelihood of tachycardia (25.4% [62/244] vs 44.3% [54/122]; P<.001) or hypertension requiring treatment (18.9% [46/244] vs 29.5% [36/122]; P=.02).

Conclusions There was no difference between dexmedetomidine and midazolam in time at targeted sedation level in mechanically ventilated ICU patients. At comparable sedation levels, dexmedetomidine-treated patients spent less time on the ventilator, experienced less delirium, and developed less tachycardia and hypertension. The most notable adverse effect of dexmedetomidine was bradycardia.

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the practice of critical care sedation has been on nurse-implemented algorithms and drug-interruption protocols to optimize drug delivery, regardless of class.[8,15,16] These protocols and algorithms are promising but not uniformly beneficial,[17,18] and their adoption into routine practice has been slow.[3,19,20]

Dexmedetomidine is an α_2 adrenoreceptor agonist with a unique mechanism of action, providing sedation and anxiolysis via receptors within the locus ceruleus, analgesia via receptors in the spinal cord, and attenuation of the stress response with no significant respiratory depression.[21,22] We hypothesized that a sedation strategy using dexmedetomidine would result in improved outcomes in mechanically ventilated, critically ill medical and surgical ICU patients compared with the standard GABA agonist midazolam. To test this hypothesis, we randomized patients in 5 countries to receive dexmedetomidine or standard sedation using midazolam infusions for up to 30 days of mechanical ventilation.

METHODS
Study Design
This prospective, double-blind, randomized trial was conducted in ICUs at 68 centers in 5 countries between March 2005 and August 2007. Because the protocol involved a dosing strategy at doses up to twice the limits approved by the US Food and Drug Administration, it was considered a phase 4 trial. The protocol was approved by the institutional review board of the study centers, and all patients or legally authorized representatives provided written informed consent. The study was designed jointly by the sponsor and investigators. Data were collected by the investigators and analyzed by a third-party commercial clinical research organization (Omnicare Inc, Covington, Kentucky). For this report, all analyses were repeated as part of an independent statistical analysis performed by one of the authors (D.W.B.) at Vanderbilt University.

Patients
Eligible patients were 18 years or older, intubated and mechanically ventilated for less than 96 hours prior to start of study drug, and had an anticipated ventilation and sedation duration of at least 3 more days. Exclusion criteria included trauma or burns as admitting diagnoses, dialysis of all types, pregnancy or lactation, neuromuscular blockade other than for intubation, epidural or spinal analgesia, general anesthesia 24 hours prior to or planned after the start of study drug infusion, serious central nervous system pathology (acute stroke, uncontrolled seizures, severe dementia), acute hepatitis or severe liver disease (Child-Pugh class C), unstable angina or acute myocardial infarction, left ventricular ejection fraction less than 30%, heart rate less than 50/min, second- or third-degree heart block, or systolic blood pressure less than 90 mm Hg despite continuous infusions of 2 vasopressors before the start of study drug infusion. Patients with renal insufficiency were randomized and treated; however, patients were discontinued if they required dialysis.

Randomization and Baseline Data Collection
Patients and all study personnel except the investigative pharmacist at each site were blinded to treatment assignment. Eligible patients were randomized 2:1 to receive dexmedetomidine to obtain more comprehensive safety data during prolonged dexmedetomidine use. Midazolam was selected as the comparator medication because it is the only benzodiazepine approved for continuous infusion and is commonly used for long-term sedation in many countries, including the United States.[2-5,17-20] All patients were centrally randomized using an interactive voice-response system and a computer-generated schedule. Detailed information regarding sedative and analgesic therapy prior to initiation of study drug, baseline demographics, and severity of illness were obtained at the time of enrollment after consent was signed.

Study Drug Administration
Each patient received study drug within 96 hours after intubation. Sedatives used before study enrollment were discontinued prior to the initiation of study drug, and patients were required to be within the Richmond Agitation and Sedation Scale (RASS)[23] target range of –2 to +1 at the time of study drug initiation. Optional blinded loading doses (up to 1 µg/kg dexmedetomidine or 0.05 mg/kg midazolam) could be administered at the investigator's discretion. The starting maintenance infusion dose of blinded study drug was 0.8 µg/kg per hour for dexmedetomidine and 0.06 mg/kg per hour for midazolam, corresponding to the midpoint of the allowable infusion dose range. Dosing of study drug was adjusted by the managing clinical team based on sedation assessment performed with the RASS a minimum of every 4 hours. Patients in either group not adequately sedated by study drug titration could receive open-label midazolam bolus doses of 0.01 to 0.05 mg/kg at 10- to 15-minute intervals until adequate sedation (RASS range, –2 to +1) was achieved with a maximum dose of 4 mg in 8 hours. If oversedation (RASS range, –3 to –5) did not respond to decreasing study drug infusion rate, the infusion was stopped until patients returned to the acceptable sedation range.

Analgesia with fentanyl bolus doses (0.5-1.0 µg/kg) could be administered as needed every 15 minutes. Intravenous bolus doses of fentanyl could also be given prior to an anticipated noxious stimulation such as chest physiotherapy or suctioning. Fentanyl patches were not permitted. No other sedatives or analgesics were allowed during the double-blind period. Intravenous haloperidol was permitted for treatment of agitation or delirium in increments of 1 to 5 mg, repeated every 10 to 20 minutes as needed. Study drug infusion was stopped at the time of extubation in both groups (required for midazolam infusions), after a maximum of 30 days, or if the investigator felt it was in the best interest of the patient.

Outcome Measures and Safety End Points

The primary end point was the percentage of time within the target sedation range (RASS score –2 to +1) during the double-blind treatment period. Secondary end points included prevalence and duration of delirium, use of fentanyl and open-label midazolam, and nursing shift assessments. Delirium-free days were calculated as days alive and free of delirium during study drug exposure. This method of calculation was used rather than an arbitrary 28-day end point, because delirium prevalence could be confounded by administration of postprotocol sedative medications after study drug was stopped. Additional a priori outcomes included duration of mechanical ventilation and length of stay in the ICU.

A daily arousal assessment was performed throughout the treatment period, during which patients within the RASS range of –2 to +1 were asked to perform 4 tasks (open eyes to voice command, track investigator with eyes, squeeze hand, and stick out tongue).[16] Patients were considered awake with successful completion of the assessment when they could perform 3 of 4 tasks. If the patient's RASS score was greater than +1 at the time of a scheduled assessment, study medication was titrated until a RASS score of –2 to +1 was achieved and then the arousal assessment was performed. If patients were oversedated to a RASS value of –3 to –5, study drug was interrupted until a RASS score of –2 to 0 was achieved and then the arousal assessment was performed. Delirium was assessed daily during the arousal assessment with patients in the RASS range of –2 to +1 using the Confusion Assessment Method for the ICU (CAM-ICU).[24]

During each shift, the bedside nurse assessed 3 components of patient care: the patient's ability to communicate, ability to cooperate with nursing care, and tolerance of the ICU environment (including endotracheal tube and mechanical ventilation). Each of the 3 components was assessed using a scale of 0 to 10 (0=patient not communicating, cooperating, or tolerating; 10=patient

communicating, cooperating, or tolerating), and a total score was defined as the sum of the 3 component scores.

Safety was assessed by monitoring laboratory test results, vital signs, electrocardiogram findings, physical examination findings, withdrawal-related events, and adverse events. Vital signs were recorded a minimum of every 4 hours, with every change of study drug dose, and at the time of intervention for adverse events. Adverse events were assessed and monitored by the principal investigator and were recorded from first dose of study drug until 48 hours after study drug discontinuation. Serious adverse events were recorded from study consent until 30 days after discontinuation of study drug. All-cause mortality was assessed for 30 days after ICU admission.

The protocol prespecified that blood pressure and heart rate values were considered adverse events if systolic blood pressure was less than 80 or greater than 180 mm Hg, diastolic blood pressure was less than 50 or greater than 100 mm Hg, or heart rate was less than 40/min or greater than 120/min. A greater than 30% change from baseline heart rate or blood pressure was also considered an adverse event. Interventions for bradycardia, tachycardia, and hypertension included titration or interruption of study drug or administration of medication; interventions for hypotension included titration or interruption of study drug, intravenous fluid bolus, or drug therapy.

Hyperglycemia was defined as at least 1 serum glucose value greater than 8.325 mmol/L (to convert to mg/dL, divide by 0.0555). Severe sepsis was defined as known or suspected infection with 2 or more systemic inflammatory response syndrome criteria and at least 1 new organ system dysfunction.[25] Infections with onset during the double-blind treatment period were identified by the clinical team managing the patient and supported by either positive culture data or empirical antibiotic administration in response to presumed or documented infection. Hyperglycemia and infections were not prespecified adverse events in the protocol.

Statistical Analysis

Sample Size Determination. To address the multiple objectives of comparing safety and efficacy during prolonged exposure to dexmedetomidine sedation, the sample size determination considered drug exposure, efficacy, and safety parameters. For the primary efficacy variable, the mean percentage of time within target sedation range was estimated to be 85% for dexmedetomidine and 77% for midazolam, based on a previous pilot study.[26] It was anticipated that 60% of patients would remain intubated for 72 hours after randomization. A minimum of 150 dexmedetomidine-treated patients exposed for at least 72 hours would allow adverse events occurring in 10% of the dexmedetomidine group to be estimated with a 95% confidence interval (CI) ±5%. An estimated 100 dexmedetomidine-treated patients were expected to remain intubated for at least 5 days. Considering each of these requirements, enrollment of 250 patients randomized to receive dexmedetomidine and 125 randomized to receive midazolam would have 96% power at an α of .05 to detect a 7.4% difference in efficacy for the primary outcome.

Efficacy and Safety Analysis. The primary efficacy and safety analyses were conducted on all randomized patients receiving any dose of study drug (**FIGURE 1**). The primary efficacy analysis (percentage of time within the target sedation range during the double-blind treatment period) was calculated by dividing the total time that the patients remained within the target RASS range (using linear interpolation to estimate RASS scores between assessments performed every 4 hours) by the amount of time the patient remained in the double-blind treatment period, multiplied by 100%. The mean difference and 95% CI between the dexmedetomidine and midazolam treatment groups were calculated and compared between treatment groups with the Mann-Whitney test. Treatment differences in nursing assessment scores were assessed with the Wilcoxon test. Com-

parisons of treatment groups for prevalence of delirium and use of rescue medications were performed using the Fisher exact test. Treatment comparisons for delirium-free days, duration of study drug, and doses of rescue medications were performed using the Mann-Whitney test.

To account for repeated assessments during double-blind treatment and the correlation between the assessments, a multivariate analysis was performed using a generalized estimating equation (GEE) incorporating an exchangeable working correlation structure to model the prevalence of delirium (100=yes, 0=no) as a function of treatment group and study day. The analysis was also per-

formed including a term for the interaction of treatment group and study day. The interaction term would be included in the final model if $P<.15$. Results from the GEE analysis were expressed as a coefficient, 95% CI, and associated P value.[27]

Time to extubation and length of ICU stay were calculated using Kaplan-Meier survival analysis, with differences between treatment groups assessed by the log-rank test. The log-rank P values for time to extubation and ICU length of stay were adjusted for multiple comparisons using the Bonferroni method. Successful extubation was defined as no reintubation within 48 hours, and time to extubation was defined from start of study drug to suc-

cessful extubation. Length of ICU stay was defined from start of study drug to time of ICU transfer order. Patients without extubation or discharge were censored at the time of study drug discontinuation. For the safety analysis, treatment comparisons for the incidence of adverse events were made using the Fisher exact test.

Statistical tests were 2-sided, and $P\le.05$ was considered statistically significant. All statistical evaluations were conducted using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). No interim analysis was planned or performed.

A secondary analysis was conducted on the entire intent-to-treat population. Patients randomized but not receiving study drug (n=9) did not have delirium or sedation assessments performed. The analysis was performed after assigning to the missing data a worst-case scenario (developed delirium on day 1, 0% time in target range, and using the 95% upper confidence limit for continuous variables). In addition, a "long-term use" subgroup was defined as patients receiving study drug for more than 24 hours. The major outcomes were also compared after restricting the analysis to those sites enrolling 5 patients or more.

RESULTS
Patient Population
A total of 375 eligible patients were randomized and 366 patients received study drug, comprising the primary analysis study population (244 patients received dexmedetomidine, 122 received midazolam). Nine patients randomized (6 in the dexmedetomidine group, 3 in the midazolam group) never received study drug, of whom 3 died and 6 had a change in clinical condition precluding participation. The long-term use population included 297 patients who received study drug for longer than 24 hours (Figure 1). Baseline characteristics were similar between treatment groups (TABLE 1). The number of patients treated by country were 294 (United States), 32 (Australia), 27 (Brazil), 11 (Argentina), and 2 (New Zealand).

Figure 1. Patient Enrollment, Randomization, and Treatment Flow
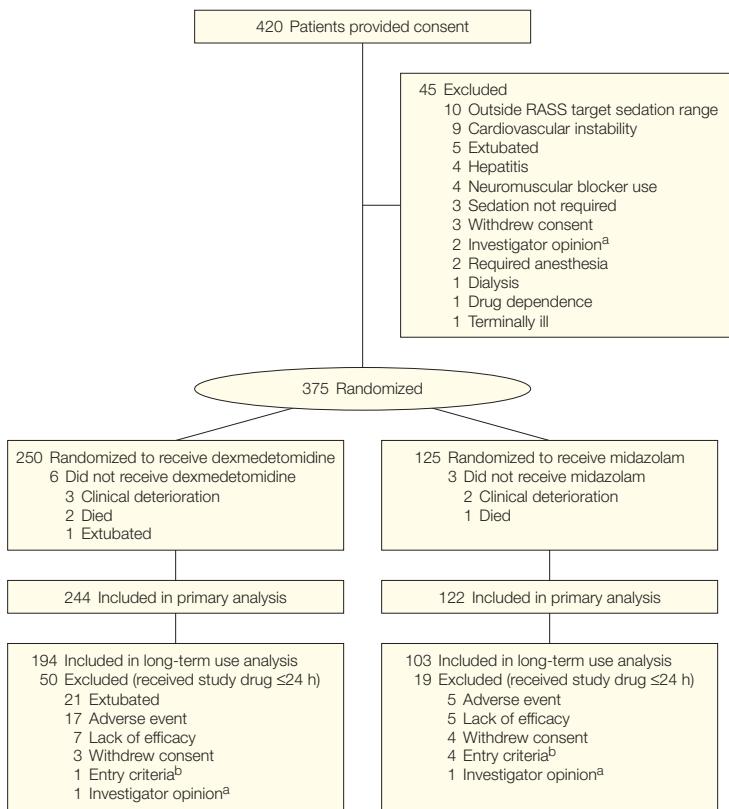
Data were analyzed using the primary analysis population (n=366) as well as the long-term use population (n=297), the group specifically requested by the US Food and Drug Administration as a means of obtaining long-term efficacy and safety data for dexmedetomidine. RASS indicates Richmond Agitation-Sedation Scale.
[a] Investigator felt that patient no longer met entry criteria (eg, extubated, no longer required sedation, required deeper sedation).
[b] Patient had new information after consent that identified an exclusion criterion (eg, need for general anesthesia, unexpected liver or cardiac disease).

Study Drug Administration and Other Sedative/Analgesic Medication Delivery

The mean (SD) maintenance infusion dose was 0.83 (0.37) μg/kg per hour for dexmedetomidine and 0.056 (0.028) mg/kg per hour for midazolam. The average dexmedetomidine maintenance dose was 0.2 to 0.7 μg/kg per hour in 95 of 244 patients (39%), 0.71 to 1.1 μg/kg per hour in 78 of 244 patients (32%), and greater than 1.1 μg/kg per hour in 71 of 244 patients (29%). Optional loading doses were administered to only 20 of 244 dexmedetomidine-treated patients (8.2%) and 9 of 122 midazolam-treated patients (7.4%). Open-label midazolam was administered to more dexmedetomidine-treated patients on the first study day (105/244 [43%] vs 37/122 [30%]; P = .02) and during the entire double-blind treatment period (153/244 [63%] vs 60/122 [49%]; P = .02). The median open-label midazolam dose was similar. The percentage of patients requiring fentanyl was similar, as was the median fentanyl dose during the double-blind period (**TABLE 2**).

Efficacy Analyses

Sedation Efficacy. There was no difference in the primary efficacy outcome, percentage of time within the target RASS range (77.3% for dexmedetomidine-treated patients and 75.1% for midazolam-treated patients; difference, 2.2% [95% CI, −3.2% to 7.5%]; P = .18). A similar percentage of patients successfully completed all daily arousal assessments and had study drug interrupted to remain in target sedation range (Table 2). The duration of study drug treatment was shorter with dexmedetomidine (P = .01), mostly because dexmedetomidine-treated patients were extubated more rapidly.

Delirium and Nursing Assessments. Results from the GEE analysis showed that the treatment group and study day were significantly associated with the prevalence of delirium. The interaction term was not significant and was not included in the final model. The final model was: delirium = 68.0 − (24.9 × dexmedetomidine) − (2.6 × study day) (95% CI for dexmedetomi-

dine, −34.2 to −15.6 [P < .001]; 95% CI for study day, −4.0 to −1.2 [P < .001]). The prevalence of delirium just before starting study drug was similar between treatment groups (Table 1). During study drug administration, the effect of dexmedetomidine treatment on delirium as measured by GEE was a 24.9% reduction (95% CI, 16% to 34%; P < .001). The prevalence of delirium was 54% (132/244) in dexmedetomidine-treated patients vs 76.6% (93/122) in midazolam-treated patients (22.6% difference; 95% CI, 14% to 33%; P < .001) (**FIGURE 2**).

This reduction of delirium remained significant for patients who were CAM-ICU–negative at study enrollment; the effect of dexmedetomidine treatment measured by GEE was

a 15.4% decrease (95% CI, 2% to 29%; P = .02), with a delirium prevalence of 32.9% (25/76) in dexmedetomidine-treated patients vs 55.0% (22/40) in midazolam-treated patients (P = .03).

For patients who were CAM-ICU–positive at baseline, the dexmedetomidine treatment effect measured by GEE was a 32.2% reduction (95% CI, 21% to 43%; P < .001), with a prevalence of 68.7% (90/131) for dexmedetomidine-treated patients vs 95.5% (63/66) for midazolam-treated patients (P < .001). Despite the shorter duration of study drug treatment, the number of delirium-free days was greater for patients treated with dexmedetomidine (2.5 days vs 1.7 days; P = .002). Haloperidol was used to treat delirium in 12.3% (30/244) of dexmedetomidine-treated patients and

Table 1. Baseline Demographics and Characteristics of Study Population

Characteristic	No. (%)		P Value
	Dexmedetomidine (n = 244)	Midazolam (n = 122)	
Age, mean (SD), y	61.5 (14.8)	62.9 (16.8)	.26
Men	125 (51.2)	57 (46.7)	.44
Weight, mean (SD), kg	88.1 (33.9)	87.8 (31.5)	.89
APACHE II score, mean (SD)[a]	19.1 (7.0)	18.3 (6.2)	.35
Medical ICU patients	212 (86.9)	103 (84.4)	.53
Surgical ICU patients	32 (13.1)	18 (14.7)	.53
Severe sepsis[b]	182 (74.6)	94 (77.1)	.70
Shock[c]	78 (32)	45 (36.9)	.35
Pneumonia	156 (63.9)	76 (62.3)	.82
Liver dysfunction[d]			
Childs-Pugh A	124 (51.0)	54 (44.3)	.27
Childs-Pugh B	115 (47.3)	67 (54.9)	.18
Creatinine, median (IQR), mg/dL	1.0 (0.7-1.4)	1.1 (0.8-1.4)	.20
Pre–study drug sedative			
Benzodiazepines	195 (79.9)	100 (82.0)	.68
Propofol	125 (51.2)	56 (45.9)	.38
Dexmedetomidine	1 (0.4)	2 (1.6)	.26
Time from ICU admission to start of study drug, median (IQR), h	40.6 (22.2-64.9)	39.3 (24.5-72.8)	.76
Delirium at enrollment (CAM-ICU–positive)[e]	138 (60.3)	70 (59.3)	.82

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II[28]; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit[24]; ICU, intensive care unit; IQR, interquartile range.
SI conversion factor: To convert creatinine values to mmol/L, multiply by 88.4.
[a]APACHE II scores recorded using worst values over previous 24 hours from time of study enrollment (mean, 40 hours following ICU admission).
[b]Known or suspected infection with 2 or more systemic inflammatory response syndrome criteria and at least 1 new organ system dysfunction.
[c]Patients with blood pressure maintained via infusions of dopamine, dobutamine, norepinephrine, epinephrine, or vasopressin prior to start of study drug.
[d]Categorized using the Childs-Pugh scoring system. Childs-Pugh A corresponds to a score of 5 through 6; B corresponds to a score of 7 through 9.
[e]Calculated from patients treated with study drug and delirium assessments at baseline (229 with dexmedetomidine, 118 with midazolam).

14.8% (18/122) of midazolam-treated patients during the double-blind treatment period.

The composite nursing assessment score for patient communication, co-operation, and tolerance of the ventilator was higher for dexmedetomidine-treated patients (21.2 [SD, 7.4] vs 19.0 [SD, 6.9]; P=.001), as were the individual scores for communication effec-tiveness (6.6 [SD, 3.0] vs 5.5 [SD, 3.1]; P<.001) and cooperation (7.0 [SD, 2.9] vs 6.1 [SD, 3.0]; P=.002), while the mean tolerance of ventilator score was not significantly different (7.6 [SD, 2.2] vs 7.4 [SD, 1.8]; P=.09).

Ventilator Time and ICU Length of Stay. More patients treated with dexmedetomidine had study drug stopped because the patient was extubated (59% [144/244] vs 45% [55/122]; P=.01). The Kaplan-Meier estimated median time to extubation was 1.9 days shorter for dexmedetomidine-treated patients (3.7 days [95% CI, 3.1 to 4.0] vs 5.6 days [95% CI, 4.6 to 5.9]; P=.01 by log-rank) (Table 2, **FIGURE 3**). The Kaplan-Meier estimated median length of ICU stay was similar (5.9 days [95% CI, 5.7 to 7.0] vs 7.6 days [95% CI, 6.7 to 8.6]; P=.24 by log-rank) (Table 2, Figure 3).

Long-term Use and Subpopulations. Results for the intent-to-treat population with assigned values (all 375 randomized patients) were similar to those from the primary analysis for time in target range (75.4% for dexmedetomidine-treated patients vs 73.3% for midazolam-treated patients), reduction of delirium in dexmedetomidine-treated patients (24.9% reduction compared with midazolam), time to extubation (3.8 days [95% CI, 3.5 to 4.0] vs 5.7 days [95% CI, 4.6 to 6.0]), and ICU length of stay (5.9 days [95% CI, 5.7 to 7.1] vs 7.7 [95% CI, 6.7 to 10.1]).

For the "long-term use" population (receiving study drug >24 hours), the percentage of time within the target RASS range was similar (80.8% for dexmedetomidine and 81% for midazolam; mean difference, −0.2% [95% CI, −5.0 to 4.7%]; P=.54), while the dexmedetomidine group experienced less delirium (treatment effect by GEE showed a 24% reduction; 95% CI,14% to 34%; P<.001), a shorter time to extubation (3.9 days [95% CI, 3.8 to 4.8] vs 5.8 days [95% CI, 4.7 to 6.2]; P=.03), and a similar ICU length of stay (6.4 days [95% CI, 5.8 to 7.5] vs 8.0 days [95% CI, 6.7 to 10.1; P=.46).

When data from low-enrolling centers (<5 patients) were excluded, 298

Table 2. Efficacy Outcomes in Patients Treated With Dexmedetomidine vs Midazolam

Outcome	No. (%)		P Value
	Dexmedetomidine (n = 244)	Midazolam (n = 122)	
Time in target sedation range (RASS score −2 to +1), mean, %[a]	77.3	75.1	.18
Patients completing all daily arousal assessments	225 (92)	103 (84.3)	.09
Patients requiring study drug interruption to maintain RASS score −2 to +1	222 (91)	112 (91.8)	.85
Duration of study drug treatment, median (IQR), d	3.5 (2.0-5.2)	4.1 (2.8-6.1)	.01
Time to extubation, median (95% CI), d[b]	3.7 (3.1-4.0)	5.6 (4.6-5.9)	.01
ICU length of stay, median (95% CI), d[b]	5.9 (5.7-7.0)	7.6 (6.7-8.6)	.24
Delirium			
Prevalence	132 (54)	93 (76.6)	<.001
Mean delirium-free days[c]	2.5	1.7	.002
Open-label midazolam use			
No. treated	153 (63)	60 (49)	.02
Dose, median (IQR), mg/kg[d]	0.09 (0.03-0.23)	0.11 (0.03-0.28)	.65
Fentanyl use			
No. treated	180 (73.8)	97 (79.5)	.25
Dose, median (IQR), µg/kg[d]	6.4 (1.8-26.3)	9.6 (2.9-28.6)	.27

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; RASS, Richmond Agitation and Sedation Scale.[23]
[a] The mean difference in percentage of time within target sedation range between the dexmedetomidine and midazolam treatment groups was calculated using the Mann-Whitney test.
[b] Calculated using Kaplan-Meier survival analysis, with differences between treatment groups assessed by the log-rank test. Log-rank P values were adjusted for multiple comparisons using the Bonferroni method.
[c] Number of days alive without delirium during study drug treatment.
[d] Calculated as the total dose during study treatment divided by body mass.

Figure 2. Daily Prevalence of Delirium Among Intubated Intensive Care Unit Patients Treated With Dexmedetomidine vs Midazolam
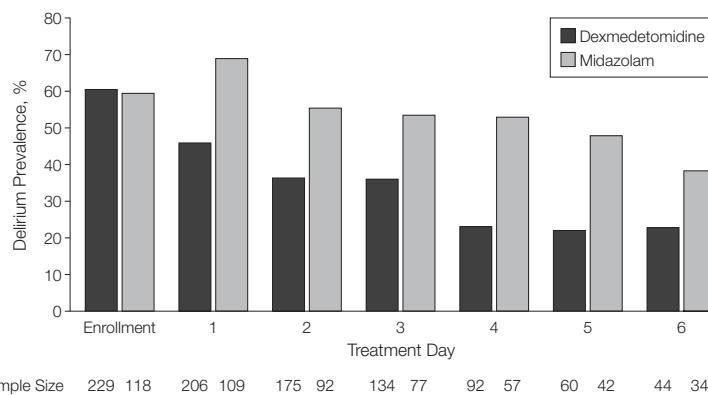
Delirium was diagnosed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).[24] At baseline, 60.3% of dexmedetomidine-treated patients and 59.3% of midazolam-treated patients were CAM-ICU–positive (P=.82). The effect of dexmedetomidine treatment was significant in the generalized estimating equation[27] analysis, with a 24.9% decrease (95% confidence interval,16%-34%; P<.001) relative to midazolam treatment. Numbers differ from those for primary analysis because patients were extubated, discharged from the intensive care unit, or had missing delirium assessments.

Figure 3. Time to Extubation and Intensive Care Unit (ICU) Length of Stay Among Patients Treated With Dexmedetomidine vs Midazolam
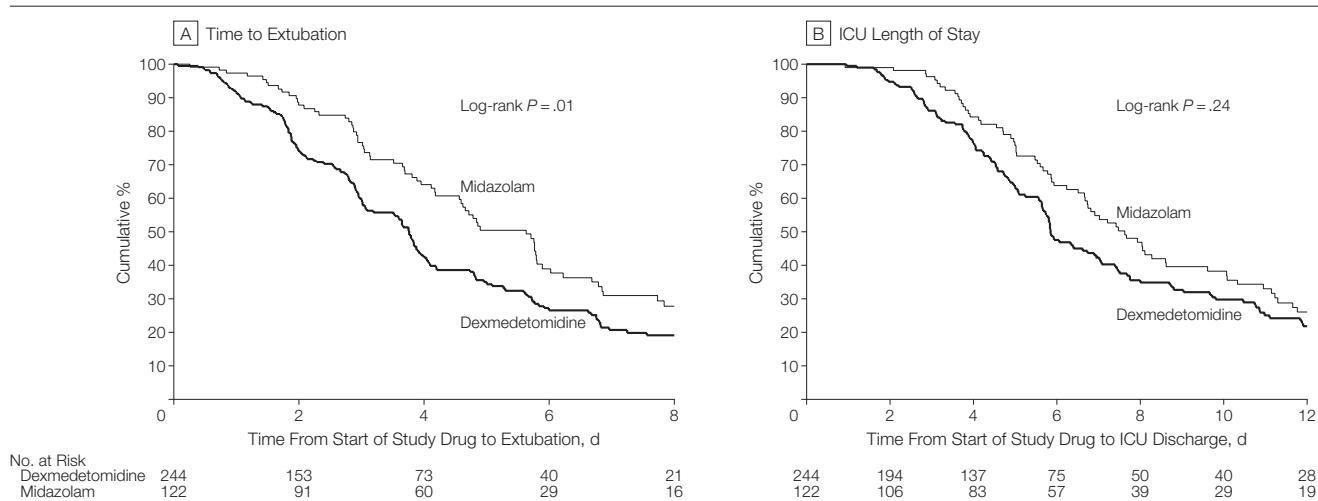
A, Time to extubation was calculated from the start of study drug to the time of extubation after which no reintubation occurred. Patients not extubated were censored at time of study drug discontinuation. The median time to extubation was 1.9 days shorter for the dexmedetomidine group than for the midazolam group (3.7 days [95% confidence interval {CI}, 3.1-4.0] vs 5.6 days [95% CI, 4.6-5.9]; $P=.01$ by log-rank test). B, Length of ICU stay was calculated from start of study drug to time of order for ICU transfer. Patients without discharge were censored at the time of study drug discontinuation. The median length of ICU stay was similar between the dexmedetomidine and midazolam groups (5.9 days [95% CI, 5.7-7.0] vs 7.6 days [95% CI, 6.7-8.6]; $P=.24$ by log-rank test).

patients were enrolled at 25 centers in 4 countries. The data analyses for these high-enrollment centers were also similar to the primary analysis. The mean percentage of time within the RASS target range was 76.5% for dexmedetomidine-treated patients and 74% for midazolam-treated patients, a difference of 2.5% (95% CI, –3.4 to 8.5; $P=.17$). The dexmedetomidine treatment effect on delirium by GEE showed a 24.2% reduction (95% CI, 14% to 34%; $P<.001$). The median time to extubation was 3.8 days (95% CI, 3.1 to 4.0) for dexmedetomidine vs 4.9 days (95% CI, 4.2 to 6.0) for midazolam ($P=.03$). The median length of ICU stay was similar (5.8 days [95% CI, 5.1 to 6.7] for dexmedetomidine and 7.7 days [95% CI, 6.7 to 10.1] for midazolam; $P=.12$).

Safety. All-cause 30-day mortality from ICU admission was not different between treatment groups (22.5% [55/244] for dexmedetomidine-treated patients vs 25.4% [31/122] for midazolam-treated patients; $P=.60$), and no death was considered related to study drug. The percentage of patients transferred alive from the ICU was also similar (81.5% [199/244] for dexme-

Table 3. Safety Outcomes During Treatment With Dexmedetomidine vs Midazolam

	No. (%)		
Outcome[a]	Dexmedetomidine (n = 244)	Midazolam (n = 122)	P Value
Cardiovascular			
Bradycardia	103 (42.2)	23 (18.9)	<.001
Bradycardia with intervention	12 (4.9)	1 (0.8)	.07
Tachycardia	62 (25.4)	54 (44.3)	<.001
Tachycardia with intervention	24 (9.8)	12 (9.8)	>.99
Hypotension	137 (56.1)	68 (55.7)	>.99
Hypotension with intervention	69 (28.3)	33 (27)	.90
Hypertension	106 (43.4)	54 (44.3)	.91
Hypertension with intervention	46 (18.9)	36 (29.5)	.02
Metabolic (hyperglycemia)	138 (56.6)	52 (42.6)	.02
Infections	25 (10.2)	24 (19.7)	.02
30-d mortality[b]	55 (22.5)	31 (25.4)	.60

[a]See "Outcome Measures and Safety End Points" for definitions and details of variables.
[b]Indicates mortality rate for 30 days after ICU admission.

detomidine-treated patients vs 81.9% [100/122] for midazolam-treated patients; $P>.99$). A similar percentage of patients stopped study drug infusions because of adverse events (16.4% [40/244] for dexmedetomidine vs 13.1% [16/122] for midazolam, $P=.44$).

More dexmedetomidine-treated patients developed adverse events related to treatment (40.6% [99/244] vs 28.7% [35/122]; $P=.03$), primarily due to a

greater incidence of bradycardia (42.2% [103/244] vs 18.9% [23/122]; $P<.001$) (**TABLE 3**). This included heart rates less than 40/ min (occurring in 5 dexmedetomidine-treated patients) and a 30% decrease from prestudy baseline (occurring in 98 dexmedetomidine-treated patients). Among dexmedetomidine-treated patients, 4.9% (12/244) required an intervention for bradycardia that included titration or interruption of study

drug infusion in 6 patients and use of atropine in 6 patients. Among midazolam-treated patients, 1 received atropine for bradycardia. A higher incidence of tachycardia occurred in the midazolam group ($P < .001$), and more hypertension requiring treatment ($P = .02$) was noted in the midazolam-treated patients.

Several adverse events not identified a priori as outcomes but monitored prospectively during the study were more prevalent in one group or the other. The incidence of infections with onset occurring during the double-blind period was less in dexmedetomidine-treated patients (10.2% [25/244] vs 19.7% [24/122], $P = .02$). These included lower rates of urinary tract infections (0% in dexmedetomidine-treated patients vs 3.3% [4/122] in midazolam-treated patients, $P = .02$) and hospital-acquired pneumonia (1.2% [3/244] in dexmedetomidine-treated patients vs 4.9% [6/122] in midazolam-treated patients, $P = .07$). As shown in Table 3, hyperglycemia occurred more frequently among dexmedetomidine-treated patients; treatment with corticosteroids was similar (65.5% [160/244] of dexmedetomidine-treated patients vs 68.9% [84/122] of midazolam-treated patients), as was insulin therapy (77.8% [190/244] of dexmedetomidine-treated patients and 74.8% [91/122] of midazolam-treated patients).

The incidence of investigator-reported adrenal insufficiency was similar (0.4% [1/244] in dexmedetomidine-treated patients vs 0% in midazolam-treated patients). Rebound hypertension and tachycardia did not occur following abrupt discontinuation of dexmedetomidine infusions. In both treatment groups, few patients experienced drug-related withdrawal events (eg, agitation, headache, hyperhidrosis, nausea, nervousness, tremor, or vomiting) after stopping study drug. Overall, 4.9% (12/244) of dexmedetomidine-treated patients and 8.2% (10/122) of midazolam-treated patients experienced at least 1 event related to withdrawal within 24 hours after discontinuing study drug ($P = .25$).

COMMENT

The primary outcome for this investigation, time in the target sedation range, was not different between patients treated with dexmedetomidine or midazolam, exceeding 75% with both medications. This finding contrasts with those of previous studies, which suggested that dexmedetomidine attained the sedation target more frequently,[12,26] but may be explained by our study design, which incorporated new standard elements for ICU sedation practice, including a light-to-moderate sedation target (RASS score −2 to +1), delirium assessment, and study drug titration or interruption every 4 hours and as part of a daily arousal assessment. The adherence to this approach is supported by the high frequency of study drug interruption by more than 90% of patients in both study groups.

Despite the similar levels of sedation attained by patients treated with dexmedetomidine and midazolam, several important differences were noted in this prospective, double-blind, randomized study. Bradycardia was more common among dexmedetomidine-treated patients, while hypertension and tachycardia were more common among midazolam-treated patients. Patients treated with dexmedetomidine developed delirium more than 20% less often than patients treated with midazolam and were removed from mechanical ventilation almost 2 days sooner.

To our knowledge, this is the first study to show that even when the elements of best sedation practice (including daily arousal, a consistent light-to-moderate sedation level, and delirium monitoring) are used for all patients, the choice of dexmedetomidine as the foundation for patient sedation further improves these important outcomes. In the context of 2 recently published smaller studies comparing dexmedetomidine with lorazepam and propofol,[12,13] these data suggest that α_2 agonists improve many important aspects of critical care, namely, less delirium and shorter duration of ventilator time.

Reductions in ventilator time, prevalence of delirium, and infection rate are especially relevant for all who care for ICU patients. The standard approach to ICU sedation is associated with delirium rates of 60% to 80% and ventilator-associated pneumonia rates of 9% to 23%.[24,29] Each additional day of delirium increases the risk of prolonged hospitalization by 20% and increases the likelihood of a poor functional status at 3 and 6 months.[30-32] Dexmedetomidine appears to be the first drug to both reduce the development of delirium and to improve the resolution of delirium if it develops in the ICU. Similarly, infections developing in ICU patients are associated with increased lengths of stay, cost, and mortality.[29] With the government considering limiting payments for preventable complications (such as delirium and nosocomial infections), aggressive effort is needed to reduce all factors contributing to these conditions.[33,34]

Dexmedetomidine binds at α_2 receptors rather than GABA receptors; this may explain the improved outcomes we and others have detected when comparing these two classes of medication.[12,13] In addition to sedation, dexmedetomidine provides analgesic effects, a lack of respiratory depression, sympatholytic blunting of the stress response, preservation of neutrophil function (compared with the neutrophil-suppressing effect of GABA-agonist medications), and may establish a more natural sleep-like state.[22,35-39]

Several important aspects related to dosing of dexmedetomidine and other medications in this investigation warrant discussion. In 61% of patients, dexmedetomidine doses exceeded the approved maximum of 0.7 µg/kg per hour, and 80% of patients received dexmedetomidine for longer than the approved maximum duration of 24 hours. These initial limits were developed in 1999 from short-term studies after general anesthesia.[40] Since then, multiple studies have suggested that patients may require higher doses and can be treated for longer than 24 hours.[41-43] This study confirms that dexmedeto-

midine infusion rates up to 1.4 µg/kg per hour for longer than 24 hours provides sedation similar to midazolam, are safe, and are associated with improved outcomes. A 2-fold greater incidence of bradycardia was seen in patients treated with dexmedetomidine, whereas midazolam-treated patients experienced a greater incidence of tachycardia and hypertension requiring treatment. Unlike the α_2 agonist clonidine, no evidence for rebound hypertension or tachycardia was detected during the 48-hour follow-up period after stopping dexmedetomidine.

Our study design allowed enrollment up to 96 hours after ICU admission and calculated Acute Physiology and Chronic Health Evaluation (APACHE) scores for the 24 hours preceding study drug administration. Severity-of-illness tools designed for use at admission underestimate the severity of illness when used 2 or 3 days after admission, and it is likely our patients were sicker than the APACHE scores suggest.[44] The high incidence of severe sepsis and shock in our patients at baseline and mortality rates of 22.5% and 25.4% (which match those in studies of severe sepsis and septic shock[45,46]) further support that these data were derived from a critically ill population of patients.

Several limitations of this study warrant discussion. The primary analysis targeted patients treated with study drug, rather than the usual intent-to-treat-as-randomized group. However, a conservative analysis of all 375 randomized patients matched the primary analysis.

Midazolam was selected as the comparator medication owing to its frequent use for long-term sedation and was administered as a continuous infusion owing to its short half-life and to facilitate maintaining the blinded nature of the study. Although midazolam is often identified as the sedative most commonly used for long-term sedation,[2,5,17] common alternatives such as lorazepam or propofol were not tested in this study. Smaller studies with different designs have compared dexmedetomidine with propofol and lorazepam, also suggesting a benefit from dexmedetomidine.[12,13]

Many centers in this study enrolled few patients, raising concern for potential bias, variability, and unbalanced center effect if only contributing to 1 study group. When centers enrolling fewer than 5 patients were excluded, 81% of our primary analysis population remained, and results from these patients matched our primary data. We excluded patients requiring renal replacement therapy to avoid the confounding effect of accumulating midazolam metabolites and dialysis clearance of medication. Analyses of dexmedetomidine and midazolam use in patients with renal dysfunction have concluded that the effect of both drugs is prolonged[47,48]; it is unknown whether the benefits of dexmedetomidine we observed would be seen in these patients.

CONCLUSIONS

This investigation (which incorporated best sedation practices including a light-to-moderate sedation level and daily arousal assessments in both study groups) showed no difference in the time patients spent within the sedation target range with dexmedetomidine or midazolam. Despite this similarity in sedation levels, dexmedetomidine shortened time to removal from mechanical ventilation and reduced the prevalence of delirium. Future studies of ICU sedation must look beyond the quality or quantity of sedation to focus on additional important clinical outcomes, including those we studied (prevalence of delirium and time of mechanical ventilation) and several our study was not powered to evaluate (ICU length of stay, rates of nosocomial infection, mortality, and long-term cognitive function).

In addition to the medication administration protocol and incorporation of best sedation practices, the choice of medication used to provide sedation for ICU patients is a fundamental component of efforts to deliver safe and effective care. Although it did not increase the time within target sedation range, dexmedetomidine appears to provide several advantages for prolonged ICU sedation compared with the GABA-agonist midazolam.

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As any change must begin somewhere, it is the single individual who will experience it and carry it through. The change must indeed begin with an individual; it might be any one of us. Nobody can afford to look around and to wait for somebody else to do what he is loath to do himself.

—Carl G. Jung (1875-1961)