ORIGINAL ARTICLE

Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis

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ABSTRACT

BACKGROUND

Guidelines currently recommend targeting light sedation with dexmedetomidine or propofol for adults receiving mechanical ventilation. Differences exist between these sedatives in arousability, immunity, and inflammation. Whether they affect outcomes differentially in mechanically ventilated adults with sepsis undergoing light sedation is unknown.

METHODS

In a multicenter, double-blind trial, we randomly assigned mechanically ventilated adults with sepsis to receive dexmedetomidine (0.2 to 1.5 μg per kilogram of body weight per hour) or propofol (5 to 50 μg per kilogram per minute), with doses adjusted by bedside nurses to achieve target sedation goals set by clinicians according to the Richmond Agitation–Sedation Scale (RASS, on which scores range from −5 [unresponsive] to +4 [combative]). The primary end point was days alive without delirium or coma during the 14-day intervention period. Secondary end points were ventilator-free days at 28 days, death at 90 days, and age-adjusted total score on the Telephone Interview for Cognitive Status questionnaire (TICS-T; scores range from 0 to 100, with a mean of 50±10 and lower scores indicating worse cognition) at 6 months.

RESULTS

Of 432 patients who underwent randomization, 422 were assigned to receive a trial drug and were included in the analyses — 214 patients received dexmedetomidine at a median dose of 0.27 μg per kilogram per hour, and 208 received propofol at a median dose of 10.21 μg per kilogram per minute. The median duration of receipt of the trial drugs was 3.0 days (interquartile range, 2.0 to 6.0), and the median RASS score was −2.0 (interquartile range, −3.0 to −1.0). We found no difference between dexmedetomidine and propofol in the number of days alive without delirium or coma (adjusted median, 10.7 vs. 10.8 days; odds ratio, 0.96; 95% confidence interval [CI], 0.74 to 1.26), ventilator-free days (adjusted median, 23.7 vs. 24.0 days; odds ratio, 0.98; 95% CI, 0.63 to 1.51), death at 90 days (38% vs. 39%; hazard ratio, 1.06; 95% CI, 0.74 to 1.52), or TICS-T score at 6 months (adjusted median score, 40.9 vs. 41.4; odds ratio, 0.94; 95% CI, 0.66 to 1.33). Safety end points were similar in the two groups.

CONCLUSIONS

Among mechanically ventilated adults with sepsis who were being treated with recommended light-sedation approaches, outcomes in patients who received dexmedetomidine did not differ from outcomes in those who received propofol. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01739933.)

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Worldwide, at least 20 million patients each year have sepsis with severe organ dysfunction,[1] with over 20% receiving mechanical ventilation.[2,3] Sedative medications are frequently used for patient comfort and safety but may potentiate acute brain dysfunction (e.g., delirium or coma) and long-term cognitive impairment.[4-10] Basic and translational studies show that among the recommended sedatives, dexmedetomidine (an alpha$_2$ receptor agonist) has antiinflammatory and bacterial clearance properties that are superior to those of gamma-aminobutyric acid (GABA) agonists, such as benzodiazepines and propofol, and also reduces neuronal apoptosis and promotes biomimetic sleep — all of which could improve clinical outcomes.[11-17] Trials comparing dexmedetomidine with benzodiazepines in adults have shown that the use of dexmedetomidine results in improvement in outcomes such as delirium, coma, and time receiving mechanical ventilation.[18,19] Patients treated with dexmedetomidine had a lower incidence of subsequent infection,[19] and the beneficial effects of dexmedetomidine, including lower 28-day mortality, were more pronounced in patients with sepsis.[18,20]

A noninferiority trial comparing dexmedetomidine with propofol in critically ill patients, about half of whom had sepsis, showed that patients who received dexmedetomidine were more interactive, but the choice of sedation did not affect the duration of mechanical ventilation, the length of stay in the intensive care unit (ICU) or hospital, or short-term mortality.[21] The differences between the sedatives with respect to the risk of acute brain dysfunction or cognitive impairment and mortality months after critical illness were unclear. Subsequent open-label trials with dexmedetomidine as the primary sedative did not show a reduction in acute brain dysfunction, a greater number of ventilator-free days, or lower mortality at 180 days than was shown with control sedative regimens (primarily propofol), although concomitant nontrial sedatives were frequently used and few patients were maintained at light sedation.[22,23]

The Society of Critical Care Medicine[24] recommends sedation with either dexmedetomidine or propofol targeted to light levels of sedation for adults receiving mechanical ventilation and continuous sedation. Given the superior immunomodulatory effects of dexmedetomidine and its benefit in patients with sepsis as compared with benzodiazepines, we designed the MENDS2 trial (Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Septic Patients with Acute Respiratory Failure) to test whether dexmedetomidine leads to better short-term and long-term outcomes than propofol in mechanically ventilated adults with sepsis.

Methods

Trial Design and Oversight

We conducted a double-blind, randomized, controlled trial at 13 medical centers in the United States. The institutional review board at each center approved the protocol (available with the full text of this article at NEJM.org). Patients or their surrogates provided written informed consent before enrollment. The trial was designed by the authors, who gathered and analyzed the data, attest to the accuracy and completeness of the data, vouch for the fidelity of the trial to the protocol, and wrote and agreed to submit the manuscript for publication. An independent data and safety monitoring board provided oversight of the trial. Pfizer supplied the dexmedetomidine trial drug but had no role in the design or conduct of the trial, analysis of the data, or writing of the manuscript. The Food and Drug Administration approved an Investigational New Drug application for dexmedetomidine administered for more than 24 hours and for doses up to 1.5 μg per kilogram per hour (see the Supplementary Appendix, available at NEJM.org). We registered the trial at ClinicalTrials.gov before enrollment began. Before group assignments were unmasked, we registered the statistical analysis plan at Open Science Framework (https://osf.io/dfyxh/) in January 2019 (with publication in March 2020).[25]

Patient Selection and Randomization

We included adults who were sequentially admitted to a medical or surgical ICU, had suspected or known infection, and were treated with continuous sedation for invasive mechanical ventilation. Patients were excluded if they had baseline severe cognitive impairment; were pregnant or breast-feeding; were blind, deaf, or unable to understand approved languages; had second-degree or third-degree heart block or persistent bradycardia requiring intervention; had an allergy to dexmedetomidine or propofol; had an indication

for benzodiazepines; were anticipated to have immediate discontinuation of mechanical ventilation; were expected to have neuromuscular blockade for more than 48 hours; were in a moribund state; or had received mechanical ventilation for more than 96 hours before meeting all inclusion criteria. Additional details on exclusion and inclusion criteria are provided in Section S1 in the Supplementary Appendix. We randomly assigned patients to receive dexmedetomidine or propofol in a 1:1 ratio using computer-generated permuted blocks stratified by enrollment site and age (<65 years vs. ≥65 years). Researchers, clinicians (except bedside nurses), patients, and families were unaware of the group assignments.

TRIAL INTERVENTIONS AND MEASUREMENTS

Investigational pharmacists prepared dexmedetomidine (5 μg per milliliter) and propofol (10 mg per milliliter) in identical intravenous fluid bags covered with opaque plastic bags to be administered in units of milliliters per hour to maintain study masking (Sections S2 and S3). Bedside nurses covered intravenous tubing with opaque coverings and verified that covers were in place before study personnel or clinicians entered patients' rooms. The trial drug was initially infused at a dose corresponding to the same sedative dosing that the patient was receiving immediately before randomization. Bedside nurses used a weight-based dosing guideline (0.15 to 1.5 μg per kilogram of actual body weight per hour for dexmedetomidine and 5 to 50 μg per kilogram of actual body weight per minute for propofol) to adjust the trial drug every 10 minutes to target sedation goals set by the clinical team and documented each adjustment and the rationale for it. The clinical team used the Richmond Agitation–Sedation Scale (RASS, on which scores range from −5 [unresponsive] to +4 [combative]),[26] to set the sedation goal, which was primarily light sedation (RASS score 0 to −2).

Administration of the trial drug was temporarily held in the event of hypotension, bradycardia, sedation deeper than the target level, spontaneous awakening trials, or surgery. The trial drug was permanently discontinued if the patient had persistent symptomatic bradycardia, new onset second- or third-degree heart block, serious allergic reactions, suspected propofol-related infusion syndrome (refractory shock, rhabdomyolysis, acidosis, and kidney failure related to high propofol exposure), or any serious adverse event related to the intervention. The trial drug was discontinued after the 14-day intervention period, extubation, or discharge from the ICU, whichever came first. Patients whose trachea was extubated and reintubated within the 14-day intervention period resumed the trial drug if sedation was indicated.

We treated pain with intermittent opioid boluses or fentanyl infusion (see Section S4 for details regarding rescue sedation, neuromuscular blockade, and treatment of agitated delirium). Additional patient care practices (e.g., administration of fluids, vasopressors, or antibiotics and extubation criteria) were based on international guideline recommendations.[24,27]

All centers performed, and investigators reinforced, the ABCDE (awakening and breathing coordination, choice of sedation, delirium monitoring and management, and early mobility) bundle,[28,29] with daily adherence recorded. In addition to care assessments made by nurses, trained research personnel assessed patients with the use of RASS for level of arousal,[26] Confusion Assessment Method for the ICU (CAM-ICU)[30] for delirium, and the Critical Care Pain Observation Tool[31] for pain; assessments were made twice daily in the ICU and then once daily after transfer from the ICU for up to 14 days or until discharge from the hospital or death. We strived to conduct delirium assessments when the patient was maximally awake. A RASS score of −4 or −5 indicated coma, and a positive CAM-ICU score indicated delirium.

Six months after randomization, research personnel assessed patients' cognition with the Telephone Interview for Cognitive Status (TICS) questionnaire[32] and a validated telephone cognitive battery,[33] functional status with the Katz Activities of Daily Living (ADL) scale[34] and the Functional Activities Questionnaire (FAQ),[35] and quality of life with the European Quality of Life–5 Dimensions (EQ-5D) survey (Section S5).[36]

TRIAL END POINTS

The primary efficacy end point was the number of calendar days alive without delirium or coma during the 14-day intervention period. Secondary efficacy end points included ventilator-free days at 28 days, death at 90 days, and global cognition at 6 months using the age-adjusted TICS total score (TICS-T score). Additional details regarding ef-

ficacy, adherence, and safety end points are provided in Section S5, along with a list of additional end points not reported here.

STATISTICAL ANALYSIS

Owing to enrollment that was slower than anticipated, the data and safety monitoring board and the National Institutes of Health approved a protocol amendment in March 2017 to lower the enrollment target from 530 patients to 420 patients receiving the trial drug to provide 85% power to detect a 1.5-day difference in days alive without delirium or coma between groups and 80% power to detect a 12 percentage-point absolute difference in mortality at 90 days, assuming an expected mortality of 30% in the propofol group. We had at least 80% power to detect a 3.9-point difference in age-adjusted TICS-T scores between groups, with a 5-point difference considered to be clinically important.

We analyzed data in the modified intention-to-treat population, which was prespecified as all patients who underwent randomization and received a trial drug. We analyzed primary and secondary end points using both univariate methods and multivariable regression models and considered adjusted analyses to be the primary analyses. We analyzed days alive without delirium and coma, ventilator-free days, and age-adjusted TICS-T scores at 6 months using proportional-odds logistic regression and analyzed death at 90 days using Cox proportional-hazards regression (adjusted for covariates listed in Section S5).

We adjusted the level of statistical significance for the primary end point analysis to $P<0.044$ to account for one prespecified planned interim analysis. The level of statistical significance for all other end points was $P<0.05$. Simple imputation was used for missing in-hospital variables and multiple imputation for partially available long-term end points to avoid bias owing to missing variables. We did not adjust for multiple comparisons in the analysis of secondary end points. We used Research Electronic Data Capture software (REDCap, Vanderbilt University) for data management and R, version 3.6.2 (R Foundation for Statistical Computing), for statistical analyses.

RESULTS

PATIENTS

From May 2013 through December 2018, we screened 4840 patients, 4402 (91%) of whom met at least one exclusion criterion (Fig. 1). Of 438 patients enrolled, 6 were subsequently found to be ineligible, 432 patients underwent randomization, and 422 began receiving dexmedetomidine (214 patients) or propofol (208 patients). The demographic and in-hospital characteristics of the patients are shown in Table 1 and Table S1.

TRIAL INTERVENTIONS

Details of trial drug dosing, dose adjustment, and sedation regimen are shown in Table 2 and Table S2. The median RASS score as assessed by the research team was −2 (interquartile range, −3.00 to −1.00) while patients were receiving a trial drug (median days of administration, 3.0 [interquartile range, 2.0 to 6.0]), indicating light sedation and ability of patients to make eye contact with only verbal stimulation (Fig. S1). The overall time spent at the target sedation was close to 60% in both groups (Fig. S2). Bedside nurses adjusted the trial drug infusion a median of 10 times (interquartile range, 5 to 21) over the duration of administration. Common reasons for adjustment of the infusion included undersedation, oversedation, and hypotension. The trial drug was temporarily held in approximately one quarter of all patients. Rescue midazolam was used in about half the patients, most often for procedural sedation or during neuromuscular blockade, and the median daily exposure on days it was administered was 4 mg (interquartile range, 2 to 11). The use of open-label propofol (received by 13% in the dexmedetomidine group and 8% in the propofol group) and dexmedetomidine (4% in the dexmedetomidine group and 3% in the propofol group) was infrequent and doses were low, indicating high adherence to the protocol. Overall, 42% of the patients received an antipsychotic medication. Soft wrist restraints during receipt of mechanical ventilation were the standard of care in our trial ICUs; thus, 96% of patients had restraints in place for a median of 3 days (interquartile range, 2 to 5). Neuromuscular blockade infusion was used in 17% of patients for a median of 1 day (interquartile range, 1 to 2) at some point while they were receiving the trial drug. Pain was well controlled in both groups according to Critical Care Pain Observation Tool scoring, and we noted high adherence to all components of the ABCDE bundle. We proactively assessed for unblinding among clinicians and research staff and found an episode of unblinding in 58 patients (14%), with a similar frequency in the two groups.

EFFICACY END POINTS

The adjusted number of days alive without delirium or coma over the 14-day intervention period was not significantly different between the dexmedetomidine group (adjusted median, 10.7 days; 95% confidence interval [CI], 8.5 to 12.5) and the propofol group (adjusted median, 10.8 days; 95% CI, 8.7 to 12.6) (odds ratio, 0.96; 95% CI, 0.74 to 1.26; P=0.79). Similarly, we found no significant differences between the dexmedetomidine and propofol groups in the number of ventilator-free days at 28 days (adjusted median, 23.7 vs. 24.0 days; odds ratio, 0.98; 95% CI, 0.63 to 1.51) or in death at 90 days (81 patients [38%] vs. 82 patients [39%]; hazard ratio, 1.06; 95% CI, 0.74 to 1.52). Results of primary and secondary efficacy end point analyses are shown in Table 3, Figure 2, and Figure S3.

We assessed more than 90% of eligible patients at 6 months after randomization (Fig. 1). Approximately 25% in each group had age-adjusted TICS-T scores that were 2 standard deviations below population norms (i.e., a score of ≤30, at a level consistent with impairment), which suggests clinically important cognitive dysfunction 6 months after critical illness. We observed no significant differences between the dexmedetomidine and propofol groups in age-adjusted TICS-T scores at 6 months (adjusted median score, 40.9 vs. 41.4; odds ratio, 0.94; 95% CI, 0.66 to 1.33). There were no clinically meaningful differences between groups in median cognitive, functional, and quality-of-life assessment scores at 6 months (Table S4).

Results of sensitivity analyses that included the 10 patients who underwent randomization but never received a trial drug (Table S5) were qualitatively similar to the results of the main analyses. Results of differential effects of the study treatment on end points according to age at enrollment, baseline cognition, and medical as compared with surgical hospitalization show that the clinical importance of these interactions appeared to be minimal (Figs. S4 through S9); however, the trial may not have been adequately powered to draw conclusions about these or other subgroups.

SAFETY END POINTS

Data on organ dysfunction and safety end points by group are shown in Tables S6 and S7, respectively. The proportions of patients who had organ dysfunction, hypotension, or severe lactic acidosis after randomization were similar in the two groups. Symptomatic bradycardia requiring discontinuation of the trial drug was similar in the two groups (Table S2). Fewer patients in the dexmedetomidine group had acute respiratory distress syndrome (ARDS) or signs of trial drug withdrawal, and fewer patients in the propofol group extubated themselves. Median plasma triglyceride levels and the proportion of patients with severely elevated levels of trigliceride (>500 mg per deciliter) were quantitatively higher in the propofol group than in the dexmedetomidine group on days 7 and 14, although these differences are unlikely to be clinically relevant. Similarly, median plasma cortisol levels at day 14 were slightly lower in the dexmedetomidine group than in the propofol group, including a higher proportion of patients with low cortisol (<20 μg per deciliter). Clinicians had access to these results without indication of group assignment and discontinued the trial drug in eight patients owing to hypertriglyceridemia. One patient had suspected propofol-related infusion syndrome (later disproved) and had the propofol discontinued.

DISCUSSION

In this multicenter, double-blind, randomized, controlled trial involving mechanically ventilated adults with sepsis who were being treated with recommended light-sedation approaches, we did not find evidence that sedation with dexmedetomidine led to more days alive without acute brain dysfunction than propofol. Furthermore, we found no difference in ventilator-free days at 28 days, death at 90 days, or global cognition (as assessed with the use of age-adjusted TICS-T scores) at 6 months between the dexmedetomidine and propofol groups. Safety end points were also similar in the two groups.

Although recent data suggest that many critically ill adults receiving mechanical ventilation may not require sedative infusions,[38,39] our trial specifically enrolled adults with sepsis who had a high severity of illness, a greater risk for ARDS, and a higher requirement for continuous sedation. It was important to better characterize the effect of greater arousability, analgesic properties, and lack of respiratory depression observed with dexmedetomidine as compared with GABAergic sedatives in this population. Data indicate meaningful differences between dexmedetomidine and

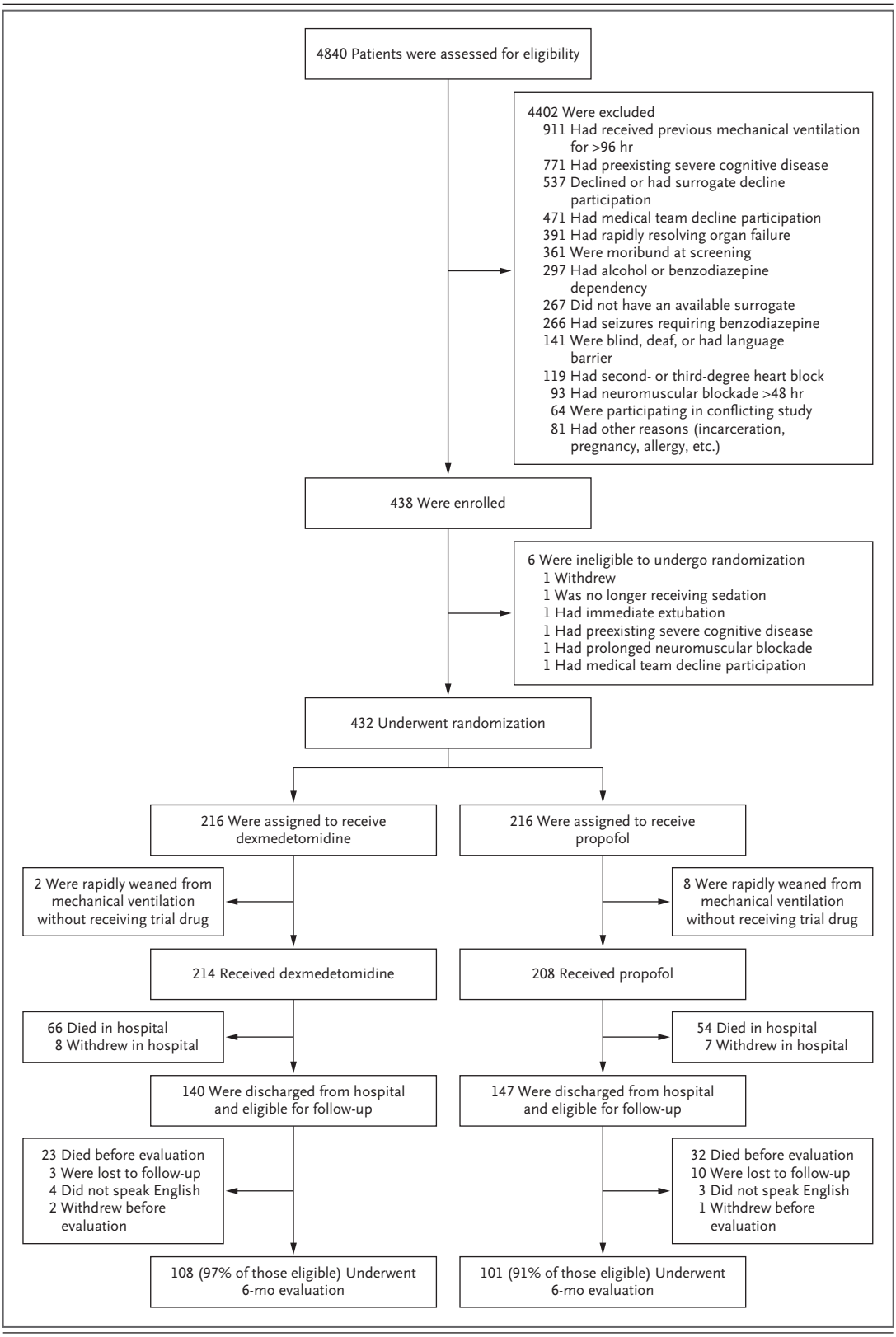


Figure 1 (facing page). Screening, Randomization, Follow-up, and Analysis.

The number of patients excluded for each criterion total more than the total number of patients excluded because some patients met more than one exclusion criterion.

GABAergic sedatives with respect to innate immunity and risk of infection, including evidence that dexmedetomidine may offer superior anti-inflammatory effects.[11-17] Despite these theoretical benefits and studies supporting the use of dexmedetomidine, the choice between dexmedetomidine and propofol alone does not appear to substantially affect patient outcomes in the complex milieu of critical illness with sepsis. Our findings, therefore, strongly reinforce current guidelines[24] that recommend the use of either dexmedetomidine or propofol for light sedation when continuous sedation is needed for adults with or without sepsis who require mechanical ventilation.

Our trial builds on other trials that have compared dexmedetomidine with propofol,[21-23,40] with important methodologic advances that include a higher degree of sedative trial drug blinding, a better separation between groups with regard to sedative exposure, and stricter adherence to light sedation approaches, with high compliance with a standardized, multicomponent sedation management bundle (i.e., the ABCDE bundle)[28,29] that has been shown to reduce mortality and improve other important outcomes. One study by Kawazoe et al.[22] randomly assigned 201 patients with sepsis who required mechanical ventilation to open-label sedation with dexmedetomidine (up to 0.7 μg per kilogram per hour) or sedation without dexmedetomidine (infusions of propofol or midazolam or both) for up to 7 days. On 1 or more study days, 29% of the dexmedetomidine group received propofol (nearly three times the crossover rate of our study) and up to 21% received midazolam. The authors found no significant difference in the number of days without delirium or coma, the number of ventilator-free days, or mortality at 28 days with dexmedetomidine use, although the trial was probably underpowered to measure a difference in mortality.

More recently, Shehabi et al.[23] performed a landmark open-label, randomized trial of dexmedetomidine (up to 1.5 μg per kilogram per hour) as compared with usual care (infusions of propofol or midazolam or both) for up to 28 days in more than 3900 patients with critical illness. The authors did not find a significant difference between the groups in the number of days without delirium or coma at 28 days, the number of ventilator-free days at 28 days, death at 90 days (including in subgroup analyses of 806 patients with suspected or confirmed sepsis), or death at 180 days. Most patients (86%) in the dexmedetomidine group received concomitant propofol for a median of 2.0 days, and 23% received midazolam for a median of 0.5 days; this lack of separation between groups limits the interpretation of the results. Despite an unmasking episode in 14% of patients and crossover in about 10% of patients in the present study, we believe that our methodologic rigor allows a more definitive conclusion that dexmedetomidine and propofol have similar efficacy with regard to acute brain dysfunction, mechanical ventilation requirement, and mortality when light sedation goals and the ABCDE bundle are used to care for critically ill mechanically ventilated adults with sepsis. Biologically, patients with sepsis should derive important benefits from dexmedetomidine because of its immunomodulatory and antiinflammatory properties; thus, it is highly unlikely that patients without sepsis would have outcomes with dexmedetomidine substantially different from those we report.

An expanding area of interest in the care of critically ill patients is the prevention of cognitive impairment, functional impairment, and decline in quality of life after hospital discharge. The study by Shehabi et al.[23] showed similar scores in cognition (as assessed with the Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE]) and quality of life (as assessed with the EQ-5D) at 180 days in the dexmedetomidine and control groups. Using a more robust cognitive assessment battery, we found clinically important cognitive dysfunction in approximately 25% of patients after sepsis and critical illness even with light sedation approaches, and the use of dexmedetomidine as compared with propofol did not alter this finding. Considering our high follow-up rates and use of a robust assessment battery, it appears that sedation choice does not affect survivorship outcomes when currently recommended sedation approaches are used.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Dexmedetomidine (N=214)	Propofol (N=208)
Median age (IQR) — yr	59 (48–68)	60 (50–68)
Female sex — no. (%)	93 (43)	88 (42)
Median body-mass index (IQR)†	30 (25–38)	29 (25–37)
Race or ethnic group — no. (%)‡		
White	188 (88)	177 (85)
Black	15 (7)	23 (11)
Latinx	12 (6)	18 (9)
Multiple or other	11 (5)	8 (4)
Median IQCODE-SF score (IQR)§	3.06 (3.00–3.23)	3.00 (3.00–3.25)
Median Charlson Comorbidities Index score (IQR)¶	2 (1–4)	2 (1–4)
Admitted to surgical ICU — no. (%)	76 (36)	72 (35)
Median APACHE II score at ICU admission (IQR)‖	27 (21–32)	27 (22–32)
Median days from ICU admission to trial enrollment (IQR)	1.21 (0.67–1.95)	1.17 (0.68–1.94)
Median days of mechanical ventilation before trial enrollment (IQR)	0.98 (0.58–1.36)	0.97 (0.61–1.54)
Median total SOFA score at trial enrollment (IQR)**	10 (8–13)	10 (8–12)
Shock, receiving vasopressor, at enrollment — no. (%)	119 (56)	102 (49)
Known or suspected source of infection — no. (%)		
Blood	92 (43)	79 (38)
Lung	116 (54)	133 (64)
Abdomen	19 (9)	20 (10)
Urinary tract	46 (21)	55 (26)
Skin or wound	23 (11)	26 (12)
Stool	12 (6)	12 (6)
Other	24 (11)	21 (10)
Infection status — no. (%)		
Infection confirmed by culture	146 (68)	132 (63)
Infection suspected but not confirmed by culture	58 (27)	68 (33)
Infection ruled out	10 (5)	8 (4)
Dexmedetomidine before enrollment — no. (%)	35 (16)	25 (12)
Propofol before enrollment — no. (%)	131 (61)	129 (62)
Benzodiazepine before enrollment — no. (%)	62 (29)	73 (35)
Opioid before enrollment — no. (%)	144 (67)	147 (71)
Antipsychotic agent before enrollment — no. (%)	24 (11)	27 (13)
Delirium at enrollment — no. (%)††	75 (35)	91 (44)
Level of arousal closest to the time of randomization — no. (%)‡‡		
Coma: RASS –5 or –4	81 (38)	74 (36)
Deep sedation: RASS –3	29 (14)	38 (18)
Light sedation: RASS –2 or –1	85 (40)	75 (36)
Awake and calm: RASS 0	13 (6)	14 (7)
Agitated: RASS +1 to +4	6 (3)	7 (3)

* Percentages may not total 100 because of rounding. Summary statistics are reported for nonmissing values. ICU denotes intensive care unit, and IQR interquartile range.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Race or ethnic group was reported by the patient or determined by the treating physicians.

§ The Informant Questionnaire on Cognitive Decline in the Elderly short form (IQCODE-SF)[37] was used to determine preexisting dementia; scores range from 1.0 to 5.0, with higher scores indicating more severe cognitive impairment.

¶ Scores on the Charlson Comorbidity Index range from 0 to 33, with higher scores indicating a higher risk of death from a coexisting illness.

‖ The Acute Physiology and Chronic Health Evaluation (APACHE II) assesses the risk of death on a scale from 0 to 71, with higher scores indicating a higher risk of death.

** The Sequential Organ Failure Assessment (SOFA) is used to track organ failure in the ICU; scores range from 0 to 24, with higher scores indicating greater severity of illness.

†† Delirium was deemed to be present when the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU, which scores delirium as either present [positive] or not present [negative]), was positive.

‡‡ The Richmond Agitation–Sedation Scale (RASS) measures levels of consciousness on a scale from –5 (unresponsive) to +4 (combative).

Table 2. Adherence and Sedation Regimen.

Outcome	Dexmedetomidine N = 214	Propofol N = 208
Median hours from meeting inclusion criteria to drug initiation (IQR)	22.4 (13.4–31.3)	22.1 (12.8–33.7)
Median hours from randomization to drug initiation (IQR)	1.3 (0.9–2.2)	1.3 (0.8–2.1)
Trial drug administration		
Median days of receipt of drug (IQR)	3.0 (2.0–5.0)	4.0 (2.0–6.0)
Median days from first meeting trial criteria to initiation of drug (IQR)	1.00 (0.00–1.00)	1.00 (0.00–1.00)
Median daily volume on days administered (IQR) — ml	119 (46–243)	131 (67–229)
Median daily dose on days administered (IQR)	0.27 μg/kg/hr (0.11–0.61)	10.2 μg/kg/min (5.5–18.4)
Median total no. of drug adjustments per patient (IQR)	9 (5–15.8)	11.5 (5.8–25)
Drug temporarily held — no. (%)*	60 (28)	57 (27)
Median no. of times drug temporarily held per patient (IQR)	1 (1–1)	1 (1–2)
Drug permanently discontinued — no. (%)	25 (12)	23 (11)
Trial or clinical team aware of the drug used — no. (%)	27 (13)	31 (15)
Withdrawal from trial during hospitalization — no. (%)	10 (5)	9 (4)
Median RASS score while receiving drug (IQR)	−2.00 (−3.00 to −1.00)	−1.95 (−3.03 to −0.98)
Percent time at target sedation level while receiving drug	57	60
Median CPOT score while receiving drug (IQR)†	0.33 (0.00–0.83)	0.31 (0.00–0.87)
Percent of days with adherence to ABCDE bundle‡		
Spontaneous awakening trial	98	98
Spontaneous breathing trial	93	95
Coordination of awakening and breathing trials	86	84
Nondrug delirium interventions	99	99
Early mobilization	91	92
Median daily fentanyl dose on days administered (IQR) — μg/hr	68 (28–119)	56 (20–95)
Midazolam exposure		
Ever used — no. (%)	114 (53)	90 (43)
Median days among users (IQR)	2.0 (1.0–4.0)	1.0 (1.0–2.0)
Median daily dose on days administered (IQR) — mg per day	3.8 (2.0–10.9)	4.0 (2.0–10.8)
Antipsychotic exposure		
Ever used — no. (%)	90 (42)	87 (42)
Median days among users (IQR)	5.0 (2.0–7.8)	4.0 (2.0–8.0)
Median daily dose on days administered (IQR) — mg§	2.2 (1.0–6.4)	3.6 (1.0–6.3)
Open-label propofol exposure		
Ever used — no. (%)	27 (13)	16 (8)
Median days among users (IQR)	2.0 (1.0–3.0)	1.5 (1.0–2.0)
Median daily dose on days administered (IQR) — μg/kg/min	10.8 (4.9–17.4)	4.8 (3.4–6.6)
Open-label dexmedetomidine exposure		
Ever used — no. (%)	9 (4)	6 (3)
Median days among users (IQR)	1.0 (1.0–2.0)	1.0 (1.0–3.2)
Median daily dose on days administered (IQR) — μg/kg/hr	0.24 (0.04–0.30)	0.26 (0.07–0.7)

* The reasons for temporary holding of the drug included oversedation, hypotension, or bradycardia; spontaneous awakening trials or times during which patients were not being sedated, were not receiving mechanical ventilation, or were in the operating room are not included.
† The Critical Care Pain Observation Tool (CPOT) is used to assess for pain by evaluating facial expression, body movement, muscle tension, and adherence to use of the ventilator if intubated or vocalization if extubated. Total scores range from 0 to 8, with scores higher than 2 indicating the presence of pain.
‡ The ABCDE bundle includes evaluations for awakening and breathing coordination, choice of sedation, delirium monitoring and management, and early mobility.
§ Values shown are in intravenous haloperidol equivalents.

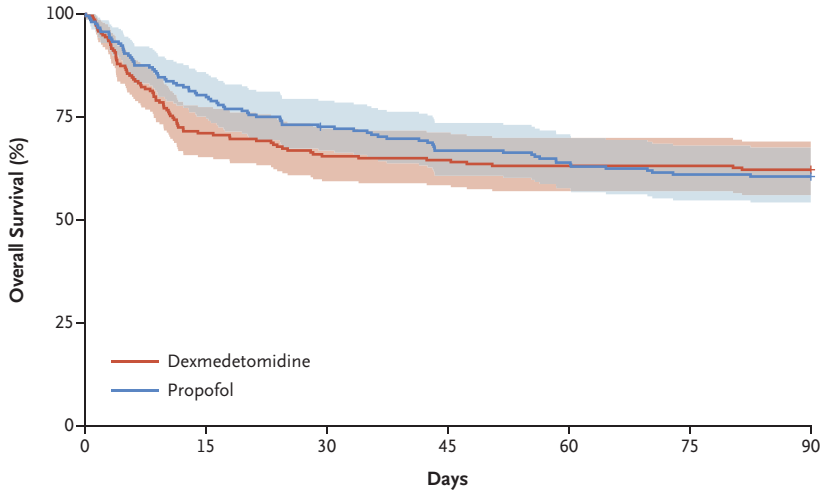
Table 3. Primary and Secondary Efficacy End Points.*

End Point	Dexmedetomidine (N=214)	Propofol (N=208)
Primary end point		
Days alive without delirium or coma at 14 days		
Unadjusted no. of days — median (IQR)	8.0 (1.0–12.8)	7.5 (1.8–11.2)
Adjusted no. of days — median (95% CI)	10.7 (8.5–12.5)	10.8 (8.7–12.6)
Adjusted odds ratio (95% CI)	0.96 (0.74–1.26)	Reference
Secondary end points		
Ventilator-free days at 28 days		
Unadjusted no. of days — median (IQR)	20.9 (0.0–26.1)	19.9 (4.2–24.9)
Adjusted no. days — median (95% CI)	23.7 (20.5–25.4)	24.0 (20.9–25.4)
Adjusted odds ratio (95% CI)	0.98 (0.63–1.51)	Reference
Death at 90 days		
Unadjusted no. of patients (%)	81 (38)	82 (39)
Adjusted hazard ratio (95% CI)	1.06 (0.74–1.52)	Reference
TICS-T score at 6 mo†		
Unadjusted score — median (IQR)	39 (28–48)	38 (30–46)
Adjusted score — median (95% CI)	40.9 (33.6–47.1)	41.4 (34.0–47.3)
Adjusted odds ratio (95% CI)	0.94 (0.66–1.33)	Reference

* Variables in adjusted analyses, except for analysis of death at 90 days, included the following: age at trial enrollment; education; baseline cognitive function as determined according to the IQCODE-SF; preexisting coexisting conditions according to the Charlson Comorbidities Index; SOFA assessment on the day of enrollment (excluding central nervous system component); level of arousal at randomization according to the RASS score closest to the time of randomization; exposure to propofol, dexmedetomidine, benzodiazepines, opioids, and antipsychotics between the time of ICU admission and midnight before enrollment; medical (vs. surgical) patient; and infection type. Variables in adjusted analyses for death at 90 days included the following: age at trial enrollment, baseline cognitive function as determined according to the IQCODE-SF, preexisting coexisting conditions according to the Charlson Comorbidities Index, SOFA assessment on the day of enrollment (excluding central nervous system component), medical (vs. surgical) patient, and infection type.

† Age-adjusted total scores on the Telephone Interview for Cognitive Status questionnaire (TICS-T) range from 0 to 100 with a mean of 50±10; lower scores indicate worse cognition, and a score of 35 or less indicates cognitive impairment.

Our trial has a number of strengths but also some notable limitations. We made every effort to mask the delivery of propofol and dexmedetomidine considering their different physical properties. Although an episode of unmasking of the group assignment to a clinician or research team member occurred in 14% of patients, adherence to blinding in our trial was higher than that reported in similar clinical trials of propofol and dexmedetomidine. We allowed clinicians to set sedation targets, achieved good separation between groups regarding sedative exposure, and had robust follow-up. In general, patients had light levels of sedation with low doses of sedative medications and concomitant opioid analgesia. This may reflect changing sedation strategies conforming to recommended practices or the need for lower sedative doses in patients with sepsis. We had some cross-contamination of sedative use, although substantially less than that in similar sedation studies, and had a rescue protocol that included the use of low-dose antipsychotic medications. The trial drug was started a median of 22 hours after the patient met all inclusion criteria, which may have limited our ability to affect outcomes. We had slower-than-anticipated enrollment, which required an adjustment of the sample size, yet had adequate power to study the questions of interest. Some exclusions were the result of clinicians not having equipoise regarding sedation for a given patient or were due to patients' (or their surrogates') decision not to agree to enrollment in the trial, factors that may affect generalizability. Overall, we



No. at Risk (Cumulative No. of Deaths)							
Dexmedetomidine	214 (0)	152 (62)	140 (74)	138 (76)	135 (79)	135 (79)	133 (81)
Propofol	208 (0)	167 (41)	150 (57)	138 (69)	132 (75)	126 (81)	125 (82)

Figure 2. Effects of Dexmedetomidine and Propofol on 90-Day Survival.

The Kaplan–Meier method was used to estimate the probability of survival. In the adjusted analyses, there was no significant difference between the trial groups with respect to death at 90 days (hazard ratio with dexmedetomidine vs. propofol, 1.06; 95% confidence interval [CI], 0.74 to 1.52). Results have not been adjusted for multiple comparisons. The shading indicates 95% confidence intervals.

believe that we studied a representative population of patients with sepsis in centers across the United States and provide more definitive evidence regarding the choice of sedation in critically ill patients with sepsis who require mechanical ventilation.

Our trial showed that among critically ill adults with sepsis who were receiving mechanical ventilation and for whom recommended light-sedation approaches were used, dexmedetomidine did not lead to better outcomes than propofol with respect to days alive without acute brain dysfunction, ventilator-free days, death at 90 days, or cognition at 6 months.

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APPENDIX

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