Weighing the Costs and Benefits of a Sedative

Hannah Wunsch, MD, MSc

CRITICALLY ILL PATIENTS TRADITIONALLY WERE HEAVily sedated for safety and to mitigate pain, anxiety, and agitation in the intensive care unit (ICU). But the approach to sedation has shifted with the recognition that heavy sedation may impede care goals such as ventilator weaning and mobilization.[1,2] A related concern is that standard sedatives may contribute to delirium, which hinders patient care, increases length of stay, and is associated with increased mortality.[3] Many approaches are used to decrease the amount of sedation given, including daily interruptions of sedation to reassess a patient, protocols to target sedation to a prespecified level, emphasis on analgesia first, and a change from default sedation for mechanically ventilated patients to individual assessment of need for sedation.[4]

In 1999, dexmedetomidine was introduced in the US market as a new sedative for use for up to 24 hours for patients undergoing mechanical ventilation. Common sedatives, such as propofol and benzodiazepines, act on the γ-aminobutyric acid (GABA) receptor and produce dose-dependent respiratory depression along with sedation. Dexmedetomidine is a highly selective α_2-agonist (closely related to clonidine) with the potential advantages of anxiolysis and some analgesia without respiratory depression or amnesia.[5] Studies comparing dexmedetomidine with benzodiazepines for longer-term (ie, greater than 24 hours) sedation suggested this drug may reduce the length of mechanical ventilation and lessen delirium.[6,7] The potential mechanisms for a decrease in delirium with a drug targeting the α_2 rather than the GABA receptor are speculative but include additional analgesia, the lack of amnesia, better approximation of natural sleep, and lack of active metabolites.[7] Yet the latest evidence suggests that dexmedetomidine is still used infrequently for general ICU patients who require continuous sedation.[8]

Why has dexmedetomidine not been embraced with greater enthusiasm in the United States? One large barrier to using dexmedetomidine is the cost. Dexmedetomidine is substantially more expensive than off-patent sedatives, such as propofol and midazolam (median per-patient drug acquisition cost was reported as $1166 for dexmedetomidine vs $60 for midazolam in one study).[9] Second, the documented benefits vs benzodiazepines are short-term and have not (yet) been translated into tangible long-term outcomes for patients.[6,7] Another barrier may be a lack of information relevant to clinicians; prior large trials have only compared dexmedetomidine with benzodiazepines, but many clinicians use propofol in preference to benzodiazepines for sedation of general ICU patients.[10,11]

In this issue of *JAMA*, Jakob et al[12] provide data from a large, multicenter randomized controlled trial (RCT) comparing dexmedetomidine with propofol (PRODEX trial), paired with a "twin" study of dexmedetomidine vs midazolam (MIDEX trial) for patients requiring prolonged mechanical ventilation. The combined studies involved 1000 patients in 75 ICUs in Europe. The design of the parallel RCTs assigned each ICU to use either midazolam or propofol for the control group based on the usual institutional practice—an important solution to decrease the likelihood that controls would receive anything other than "usual" care.

Both studies had 2 primary objectives. The first was to test the noninferiority of dexmedetomidine with regard to the ability to achieve a preselected level of sedation. The outcome was time spent at a target sedation level using the Richmond Agitation-Sedation Scale (RASS) without the need for any rescue medication.[13] The target chosen was broad: −3 (movement or eye opening to voice, but no eye contact) to 0 (alert and calm). This target was successfully met in the 2 trials, demonstrating that dexmedetomidine could keep patients in the same general sedation range as both midazolam and propofol.

The second objective was to test whether the use of dexmedetomidine was associated with a decreased duration of mechanical ventilation (including noninvasive). Other outcomes measured included time to extubation (until re-

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moval of endotracheal tube) and length of ICU and hospital stay. Dexmedetomidine shortened the time to extubation compared with propofol but did not reach statistical significance for shortening total duration of mechanical ventilation, presumably due to differences in use of noninvasive ventilation, imputation of data missing or data for patients who died, or both. Compared with midazolam, dexmedetomidine shortened both time to extubation and total duration of mechanical ventilation, confirming previous findings.[7] The other measure often reported in studies of dexmedetomidine is delirium.[6,7] Although these new trials did not provide routine standardized assessments of delirium, both studies found that patients who received dexmedetomidine had a greater ability to interact, communicate pain, and cooperate with care. These domains were measured using the components of a visual analogue scale assessed by the nurse during each shift.

Sedation studies are difficult to conduct. Any single study can only examine one approach to using a medication, in this case discontinuing patients' use of a standard sedative to start dexmedetomidine.[12] Unlike comparisons of medications such as antihypertensives, for which there may be a single immediate goal (reduction of blood pressure), sedation involves many dimensions, and the goals of treatment may include analgesia, anxiolysis, amnesia, hypnosis, or treatment of psychosis. Dexmedetomidine has now been compared directly with benzodiazepines,[6,7] antipsychotics,[14] opiates,[15] and propofol,[12] highlighting the fact that dexmedetomidine is not a unidimensional medication. To address this issue, PRODEX and MIDEX include an enormous amount of information measured across many domains, from basics such as length of stay to more complex measurements, such as tolerance of the endotracheal tube, adverse events, and neurocognitive events requiring treatment.

Blinding is also a challenge. Some aspects of blinding in sedation studies are purely practical: for example, propofol is in a lipid emulsion, and even a single drop visible at the end of the IV tubing will reveal the identity of the medication. The PRODEX trial was carefully designed with opaque tubing; connection of infusions by independent personnel; and a second, dummy infusion. But the different quality of the sedation may be perceived by caregivers and is impossible to mask.

A related issue that is perhaps the largest concern with studies of dexmedetomidine is achieving equivalent levels of sedation in comparison groups when blindly using different classes of medications. Patients who received propofol and midazolam were on average more sedated than patients receiving dexmedetomidine, even though all were in the broad target RASS range. This may be interpreted as "proof" that dexmedetomidine makes it easier to keep patients only lightly sedated but may actually be due to a mismatch in the dosing.[16] In attempting to choose equivalent doses, studies that have used blinding to date have often paired relatively low doses of dexmedetomidine with doses of benzodiazepines or propofol that seem likely to cause a deeper level of sedation, as occurred in both of these control groups.[12]

A final concern is what constitutes a meaningful outcome in sedation studies. Short-term mortality is unlikely to be affected by sedative choice, although most clinicians feel it is still important to measure in studies of critically ill patients.[6,7] Other, meaningful outcome measurements may focus on improvements in short- or long-term morbidity or reductions in costs of care.[17] Most patients, even if still in an ICU, would prefer not to be receiving mechanical ventilation. Therefore, decreasing time to extubation can be important to patients. The ability of clinicians to communicate more effectively with patients may also be a strong rationale for choosing dexmedetomidine. Benefits of enhanced communication may include better overall pain control and facilitation of earlier mobilization and rehabilitation, which may ultimately improve long-term outcomes.[2] Therefore, future studies of sedation might be paired with other ICU initiatives and focus on measurements of long-term patient-centered outcomes, such as mental health, physical well-being, and ability of survivors to perform activities of daily living many months after hospital discharge.[17]

Reducing the duration of use of any ICU resource in critically ill patients is often equated with cost savings. One analysis of prior trial data (vs midazolam) concluded that, despite the higher acquisition cost of dexmedetomidine, large savings may be associated with its use because of decreased duration of mechanical ventilation and possible decreased length of ICU stay.[9] But large cost savings are unlikely: decreasing duration of mechanical ventilation or ICU stay usually saves far less than anticipated because of the high fixed costs of intensive care.[18] However, cost structures do differ depending on the ICU population. Greater adoption of dexmedetomidine has occurred in the cardiac surgery population.[8] This adoption likely occurred because the majority of these patients only require short-term mechanical ventilation, which allows clinicians to use dexmedetomidine in line with US Food and Drug Administration guidelines. But this choice may also make economic sense because even a few hours less time mechanically ventilated could translate into tangible economic benefit for a hospital, if discharging patients a little faster allows for an increase in the volume of cardiac surgery cases.

How do the current studies assist clinicians? These 2 RCTs provide important evidence that dexmedetomidine is an effective sedative compared with both midazolam and propofol, and its use may be associated with decreased time to extubation, easier communication with patients, and better assessment of pain. But with the focus on cost containment at many hospitals, consideration of expense may preclude broad use without more

tangible long-term outcome data and without confirmation that the benefits are due to the choice of sedative and not solely the lighter sedation levels achieved. Dexmedetomidine comes off patent in the United States in 2013. When there is no longer a need to weigh the drug acquisition costs, even uncertain improvements in the patient experience should be justification enough for broader use of dexmedetomidine in the ICU.

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Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation
Two Randomized Controlled Trials

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S EDATION IN INTENSIVE CARE PA-
tients is assumed to reduce dis-
comfort from care interven-
tions, increase tolerance of
mechanical ventilation, prevent acci-
dental removal of instrumentation, and
reduce metabolic demands during car-
diovascular and respiratory instabil-
ity.[1] Long-term sedation may have se-
rious adverse effects, such as prolonged
mechanical ventilation,[2] coma,[3] de-
lirium,[4] delusional memories and post-
traumatic stress disorder,[5,6] impaired
cognitive function,[7] prolonged hospi-
talization,[2,3,8,9] increased costs,[2,3,8] and
mortality.[9] Daily sedation stops,[3] seda-
tion protocols,[3,8] spontaneous breath-
ing trials and early mobilization,[9,10] or
primary use of opiates without other
sedation[11] may help reduce these
complications.

Current sedatives are problematic in
long-term sedation. Benzodiazepines
and propofol accumulate unpredict-
ably.[12,13] High-dose or prolonged propo-
fol use may cause potentially fatal
propofol infusion syndrome.[14] Dexme-
detomidine, a sedative with high

Context Long-term sedation with midazolam or propofol in intensive care units (ICUs) has serious adverse effects. Dexmedetomidine, an α_2-agonist available for ICU sedation, may reduce the duration of mechanical ventilation and enhance patient comfort.

Objective To determine the efficacy of dexmedetomidine vs midazolam or propofol (preferred usual care) in maintaining sedation; reducing duration of mechanical ventilation; and improving patients' interaction with nursing care.

Design, Setting, and Patients Two phase 3 multicenter, randomized, double-blind trials carried out from 2007 to 2010. The MIDEX trial compared midazolam with dexmedetomidine in ICUs of 44 centers in 9 European countries; the PRODEX trial compared propofol with dexmedetomidine in 31 centers in 6 European countries and 2 centers in Russia. Included were adult ICU patients receiving mechanical ventilation who needed light to moderate sedation for more than 24 hours (midazolam, n=251, vs dexmedetomidine, n=249; propofol, n=247, vs dexmedetomidine, n=251).

Interventions Sedation with dexmedetomidine, midazolam, or propofol; daily se-
dation stops; and spontaneous breathing trials.

Main Outcome Measures For each trial, we tested whether dexmedetomidine was noninferior to control with respect to proportion of time at target sedation level (mea-
sured by Richmond Agitation-Sedation Scale) and superior to control with respect to duration of mechanical ventilation. Secondary end points were patients' ability to com-
municate pain (measured using a visual analogue scale [VAS]) and length of ICU stay. Time at target sedation was analyzed in per-protocol population (midazolam, n=233, vs dexmedetomidine, n=227; propofol, n=214, vs dexmedetomidine, n=223).

Results Dexmedetomidine/midazolam ratio in time at target sedation was 1.07 (95% CI, 0.97-1.18) and dexmedetomidine/propofol, 1.00 (95% CI, 0.92-1.08). Median du-
ration of mechanical ventilation appeared shorter with dexmedetomidine (123 hours [IQR, 67-337]) vs midazolam (164 hours [IQR, 92-380]; P=.03) but not with dexmedetomi-
dine (97 hours [IQR, 45-257]) vs propofol (118 hours [IQR, 48-327]; P=.24). Patients' interaction (measured using VAS) was improved with dexmedetomidine (estimated score difference vs midazolam, 19.7 [95% CI, 15.2-24.2]; P<.001; and vs propofol, 11.2 [95% CI, 6.4-15.9]; P<.001). Length of ICU and hospital stay and mortality were similar. Dex-
medetomidine vs midazolam patients had more hypotension (51/247 [20.6%] vs 29/ 250 [11.6%]; P=.007) and bradycardia (35/247 [14.2%] vs 13/250 [5.2%]; P<.001).

Conclusions Among ICU patients receiving prolonged mechanical ventilation, dex-
medetomidine was not inferior to midazolam and propofol in maintaining light to mod-
erate sedation. Dexmedetomidine reduced duration of mechanical ventilation com-
pared with midazolam and improved patients' ability to communicate pain compared with midazolam and propofol. More adverse effects were associated with dexmedeto-
midine.

Trial Registration clinicaltrials.gov Identifiers: NCT00481312, NCT00479661

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α_2-adrenoreceptor affinity and action in the locus ceruleus, is an alternative for sedation in intensive care units (ICUs). Dexmedetomidine may enhance patient safety and comfort in long-term sedation. It reduced the incidence of coma and delirium when compared with lorazepam[15] and—in a pilot study—reduced duration of mechanical ventilation when compared with propofol or midazolam.[16] A multicenter trial in predominantly medical ICU patients found earlier extubation and reduced delirium with dexmedetomidine compared with midazolam.[17] However, a recent meta-analysis presented inconclusive results for the effect of dexmedetomidine on duration of mechanical ventilation and ICU stay.[18] Most clinicians and centers do not consider midazolam and propofol as equivalent alternatives for long-term sedation.

We designed 2 large, parallel, randomized controlled multicenter trials to compare dexmedetomidine with either midazolam or propofol, according to the preferred usual sedation of study centers. The study designs were identical except for the usual-care control drug. We included higher doses and longer treatment than currently approved for dexmedetomidine. We assessed whether dexmedetomidine is noninferior to midazolam or propofol in maintaining mild to moderate sedation and offers benefits in terms of reduced mechanical ventilation and ICU stay and patients' ability to communicate during sedation.

METHODS

These 2 phase 3, European, multicenter, randomized, double-blind studies conducted in 2007 through 2010 compared midazolam with dexmedetomidine (MIDEX trial; 44 centers in 9 European countries) and propofol with dexmedetomidine (PRODEX trial; 31 centers in 6 European countries and 2 in Russia) and were approved by the respective ethics committees (eAppendix, available at http://www.jama.com). Written informed consent was obtained from the patient's family, a le-

gal representative, or both. An independent data safety monitoring board had full access to the ongoing unblinded data and made regular recommendations to the sponsor and steering committee, based on the risk-benefit evaluation, regarding continuation, adjustment, or termination of the 2 trials.

The main inclusion criteria were age 18 years or older, invasive mechanical ventilation, clinical need for light to moderate sedation (target sedation Richmond Agitation-Sedation Scale [RASS] score was from 0, alert and calm, to –3, responds to verbal stimulation by movement or eye opening to voice but no eye contact[19]) using midazolam or propofol infusion expected to last for 24 hours or longer after randomization, and randomization within 72 hours of ICU admission and within 48 hours of starting continuous sedation.

The main exclusion criteria were acute severe neurological disorder, mean arterial pressure less than 55 mm Hg despite appropriate intravenous volume replacement and vasopressors, heart rate less than 50/min, atrioventricular-conduction grade II or III (unless pacemaker installed), and use of α_2 agonists or antagonists within 24 hours prior to randomization. The most common reasons that patients were excluded were that they were not ventilated, they were expected to need less than 24 hours sedation, or they had an acute severe neurological disorder (complete list of exclusion criteria in eAppendix).

Randomization and Masking

Eligible study participants were randomized 1:1 by a central interactive voice-response system funded by the sponsor to either continue their current standard care (midazolam [MIDEX trial] or propofol [PRODEX trial]) or switch to dexmedetomidine. Randomization was stratified for study center in blocks of 4. All patients and study personnel were masked to treatment allocation. Treatments were administered in a double-dummy design, with 0.9% sodium chloride as dummy for all treatments. Propofol and propofol dummy were pre-

pared, connected, and removed by independent personnel and infused with nontransparent black syringes, infusion tubings, and connectors.

Study Drugs and Concomitant Treatment

Study treatments were titrated to individual sedation targets. Depth of sedation was assessed using RASS scores,[19] which range from –5 (unarousable) to +4 (combative) (eAppendix); target RASS score was determined before starting study treatment and at daily sedation stops. Assessment of RASS score was performed every 2 hours and prior to any dose of rescue therapy. Six dose levels of each study drug covered the full dose range (dexmedetomidine, 0.2-1.4 µg/kg per hour; midazolam, 0.03-0.2 mg/kg per hour; propofol, 0.3-4.0, mg/kg per hour). Study treatments were infused without loading dose at a dose matching the prerandomization dose of midazolam (MIDEX trial) or propofol (PRODEX trial) for 1 hour. Thereafter, study drugs were titrated by the patient's nurse stepwise to maintain the target RASS score (eAppendix).

Pain was treated with fentanyl boli. Rescue medication boli could be given if needed to achieve target RASS score (first-line rescue propofol in the MIDEX trial and midazolam in the PRODEX trial; further rescue medication decided by treating clinician). Need for resedation and continued ventilation was assessed after a daily sedation stop and spontaneous breathing trial. Study medication was continued up to a maximum of 14 days from randomization and stopped at the time of extubation. Patients were followed up for 45 days.

Outcomes

The first primary efficacy end point was the proportion of time in target sedation range (RASS score, 0 to –3) without use of rescue therapy of the total duration of study drug infusion; the other was duration of mechanical ventilation from randomization until patients were free of mechanical ventilation (including noninvasive) without reinstitution for the following 48 hours.

Secondary efficacy outcomes were length of ICU stay from randomization until medically fit for discharge and nurses' assessment of arousal, ability to cooperate with care, and ability to communicate pain[16] using visual analogue scales (VAS). The follow-up visit occurred on day 45 after randomization. (Refer to the eAppendix for more prespecified end points and safety monitoring.)

Statistical Methods

The planned enrolment was 500 participants in each trial. Based on a pilot study,[16] we assumed an overall 64% of time in target range of sedation without using rescue medication. A sample size of 450 in each trial gives 90% power to reject a 15% inferiority of dexmedetomidine to standard sedation using a 2-sided 95% confidence interval for the estimated ratio of dexmedetomidine to standard care.

Proportion of time within RASS target without rescue medication was analyzed in the per-protocol population to avoid bias toward noninferiority using a variance analysis model with fixed effects for treatment and country. Noninferiority margin was defined as 15%; ie, the lower 95% CI of the estimated dexmedetomidine-to-standard-care ratio of proportion of time in range must be above 0.85. Variance estimate of the ratio was calculated from the estimated covariance matrix. A sensitivity analysis using the intention-to-treat population was also performed.

The intention-to-treat population, including all randomized patients, was used for all other efficacy variables to analyze superiority. Safety was analyzed in patients who received any study drug. Length of ICU stay was until patients were judged medically fit for discharge. The primary analysis of the duration of mechanical ventilation, length of ICU stay, time to extubation, and length of hospital stay was based on a Cox proportional hazards regression model, stratified by country. The proportional hazards assumptions were only fulfilled for length of hospital stay and length of ICU stay in the propofol

vs dexmedetomidine study. Use of alternative tests was predefined in the analysis plan; therefore, the Gehan-Wilcoxon test was used post hoc. Calculation of descriptive medians and interquartile ranges excluded censored cases. Results for the VAS were analyzed using analysis of covariance, adjusting for country and baseline value. (For imputation rules, see the eAppendix.) Proportional analyses for longitudinal data were based on a generalized estimating equation model with factors for treatment, time, and country.

All data are presented as median and interquartile range (IQR) unless indicated otherwise. A 2-sided significance level of .05 was used in all treatment comparisons. Proportionality assumption was tested on a .10 level. SAS statistics software version 9.1 was used.

RESULTS

The intention-to-treat populations included 249 and 251 patients in the dexmedetomidine and midazolam groups (MIDEX trial) and 251 and 247 patients in the dexmedetomidine and propofol groups (PRODEX trial), respectively (**FIGURE 1**). Diagnostic groups and severity of organ failures[20] at baseline were comparable between the treatment groups (**TABLE 1**). In the MIDEX trial, 53 midazolam patients (21.1%) and 68 dexmedetomidine patients (27.3%) died between randomization and follow-up at day 45 ($P=.12$). In the PRODEX trial, 48 propofol patients (19.4%) and 43 dexmedetomidine patients (17.1%) died during this period ($P=.56$).

Patients in MIDEX received less dexmedetomidine compared with patients in PRODEX (**TABLE 2**). Noninferiority of dexmedetomidine vs standard care was confirmed in both studies (time at target sedation without rescue medication: midazolam, 56.6%, vs dexmedetomidine, 60.7%; propofol, 64.7%, vs dexmedetomidine, 64.6%). The estimated ratio of dexmedetomidine vs midazolam in time at target sedation was 1.07 (95% CI, 0.97-1.18; $P=.15$), and of dexmedeto-

midine vs propofol, 1.00 (95% CI, 0.92-1.08; $P=.97$) (eFigure 1). For the intention-to-treat population, the estimated ratios were dexmedetomidine/midazolam, 1.09 (95% CI, 0.99-1.19) and dexmedetomidine/propofol, 0.97 (95% CI, 0.89-1.04). Dexmedetomidine patients had higher actual RASS scores in both studies ($P<.001$) (Table 2 and eTable 1).

Study drug discontinuation rates were similar in dexmedetomidine and standard care patients (midazolam, 50/250 [20%], vs dexmedetomidine, 60/249 [24%]; propofol, 58/247 [23%], vs dexmedetomidine, 71/251 [28%]), but discontinuation due to lack of efficacy was more frequent in dexmedetomidine patients (midazolam, 10/250 [4%], vs dexmedetomidine, 23/249 [9%]; $P=.02$; propofol, 13/247 [5%], vs dexmedetomidine, 36/251 [14%]; $P<.001$). Lack of efficacy within the first 24 hours was less frequent in the midazolam vs dexmedetomidine study (5 of 23 instances) than in the propofol vs dexmedetomidine study (15 of 36 instances).

The median duration of mechanical ventilation (including noninvasive ventilation) in MIDEX was 164 hours (IQR, 92-380 hours) for midazolam and 123 hours (IQR, 67-337 hours) for dexmedetomidine (Gehan-Wilcoxon $P=.03$). In PRODEX, it was 118 hours (IQR, 48-327 hours) for propofol and 97 hours (IQR, 45-257 hours) for dexmedetomidine (Gehan-Wilcoxon $P=.24$) (**FIGURE 2**). The median time to extubation in MIDEX was 147 hours (IQR, 81-325 hours) for midazolam and 101 hours (IQR, 65-313 hours) for dexmedetomidine (Gehan-Wilcoxon $P=.01$). In PRODEX, it was 93 hours (IQR, 45-286 hours) for propofol and 69 hours (IQR, 39-184 hours) for dexmedetomidine (Gehan-Wilcoxon $P=.04$) (eFigure 2 and 3).

The median length of stay in the ICU from randomization until the patient was medically fit for discharge was not significantly different in the 2 studies (midazolam, 243 hours [IQR, 140-630 hours], vs dexmedetomidine, 211 hours [IQR, 115-831 hours]; propofol, 185 hours [IQR, 93-520 hours],

vs dexmedetomidine, 164 hours [90-480 hours]) (Figure 2). There were no significant differences between dexmedetomidine and standard care in length of hospital stay (eAppendix and eTables 2 through 9).

Patients receiving dexmedetomidine were more arousable, more cooperative, and better able to communicate their pain than patients receiving either midazolam or propofol ($P \le .001$ for each component separately and for total VAS score) (**TABLE 3**).

Sedation stops in the MIDEX trial were performed on 93.3% (midazolam) and 89.7% (dexmedetomidine) of eligible study days when no contraindication existed; in the PRODEX trial, sedation stops were performed on 90.1% (propofol) and 89.0% (dexmedetomidine) of days (Table 2). The most common reasons to restart sedation after a sedation stop were poor tolerance of the endotracheal tube or mechanical ventilation, agitation or anxiety, and cardiovascular instability

(eTable 10). Changes in serum glucose over time were not different between treatments in any of the studies (eTable 11).

In the MIDEX trial, the adverse event hypotension was recorded in 29 of 250 midazolam patients (11.6%) vs 51 of 247 dexmedetomidine patients (20.6%) ($P = .007$). Bradycardia was reported in 13 of 250 midazolam patients (5.2%) and in 35 of 247 dexmedetomidine patients (14.2%) ($P < .001$). In the PRODEX trial, hypotension and bradycardia were re-

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Figure 1. Flow Diagrams for the Dexmedetomidine vs Midazolam (MIDEX) and Dexmedetomidine vs Propofol (PRODEX) Trials
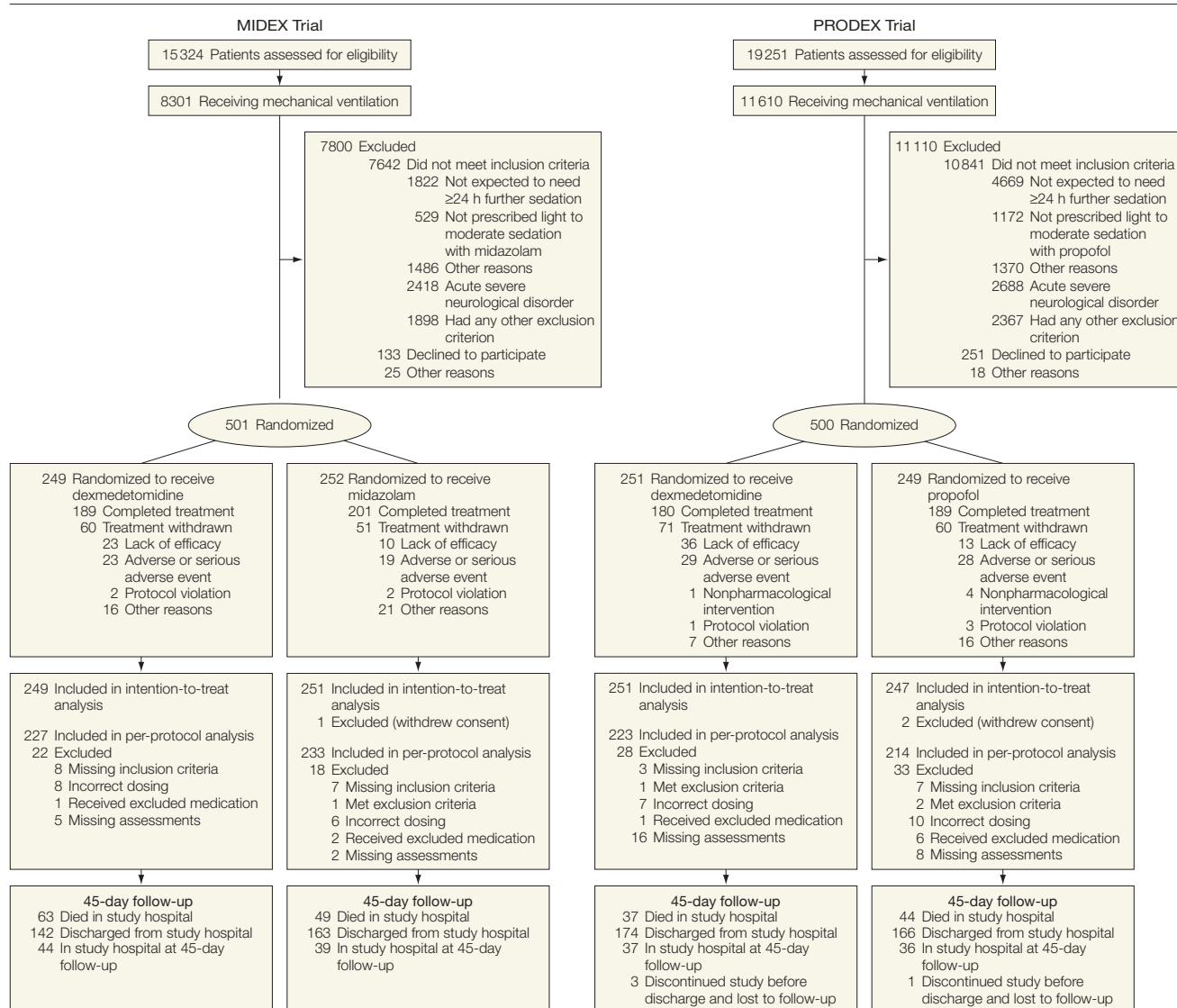
For patients who did not meet inclusion criteria, and for each patient withdrawn from treatment after randomization, more than 1 reason could apply. Patients who withdrew their consent (1 in the midazolam group and 2 in the propofol group) denied any use of their data in the analyses.

Table 1. Demographics, Diagnostic Groups, and Severity of Organ Failures at Baseline

	Dexmedetomidine vs Midazolam Study (MIDEX)			Dexmedetomidine vs Propofol Study (PRODEX)		
	Dexmedetomidine (n = 249)	Midazolam (n = 251)	P Value[c]	Dexmedetomidine (n = 251)	Propofol (n = 247)	P Value[c]
Male, No. (%)	153 (61.4)	175 (69.7)	.06	160 (63.7)	166 (67.2)	.45
Age, median (IQR), y	65 (55-74)	65 (55-74)	.98	65 (51-75)	65 (51-74)	.93
SAPS II, median (IQR)[a]	46 (36-56)	45 (34-56)	.53	48.0 (36-55)	44.5 (35-55)	.37
Main reason for admission to ICU, No. (%)						
Medical	182 (73.1)	171 (68.1)	.19	137 (54.6)	143 (57.9)	.38
Surgical	55 (22.1)	58 (23.1)		92 (36.7)	77 (31.2)	
Trauma	12 (4.8)	22 (8.8)		22 (8.8)	27 (10.9)	
Any infection at ICU admission, No. (%)	145 (58.2)	124 (49.4)	.049	136 (54.2)	127 (51.4)	.59
Organ failures (SOFA score >2), No. (%)						
Respiratory	149 (59.8)	154 (61.4)	.78	165 (65.7)	156 (63.2)	.58
Cardiovascular	152 (61.0)	151 (60.2)	.86	156 (62.2)	161 (65.2)	.52
Renal	37 (14.9)	42 (16.7)	.62	24 (9.6)	23 (9.3)	>.99
Coagulation	19 (7.6)	19 (7.6)	>.99	11 (4.4)	18 (7.3)	.18
Liver	2 (0.8)	3 (1.2)	>.99	1 (0.4)	1 (0.4)	>.99
Total SOFA score, median (IQR)[b]	7.0 (5.0-9.0)	7.0 (4.0-9.0)	.89	7.0 (5.5-9.0)	7.0 (5.0-9.0)	.88

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.
[a] The SAPS II range of possible values is 0-163; higher values indicate greater illness. The score was collected only after the protocol's first amendment requested it; the numbers of patients for each of the groups were 189, 186, 215, and 222, respectively.
[b] Sum of the SOFA scores excluding the central nervous system score (range of possible values: 0-20; higher scores indicate greater illness).
[c] For categorical variables, analyses used the Fisher exact test, and for continuous variables, analysis of variance.

Table 2. Details of Study Drug Administered and Sedation Stops

	Dexmedetomidine vs Midazolam Study (MIDEX)			Dexmedetomidine vs Propofol Study (PRODEX)		
	Dexmedetomidine (n = 249)	Midazolam (n = 251)	P Value	Dexmedetomidine (n = 251)	Propofol (n = 247)	P Value
Study drug treatment, median (IQR)						
Duration of infusion, h[a]	42 (23 to 72)	43 (24 to 92)	.15	42 (22 to 72)	47 (25 to 103)	<.001
Dose of study drug, μg/kg/h or mg/kg/h[a]	0.450 (0.273 to 0.756)	0.062 (0.041 to 0.098)		0.925 (0.673 to 1.170)	1.752 (1.211 to 2.424)	
Patients receiving rescue sedation, No. (%)	109 (43.8)	114 (45.4)	.72	182 (72.5)	159 (64.4)	.05
Total dose of rescue sedation, median (IQR), mg[b]	195 (50 to 440)	120 (60 to 300)	.32	17 (6.0 to 41.0)	14 (5.0 to 28.5)	.02
Patients receiving fentanyl, No.	190	207	.10	194	194	.75
Cumulative dose, median (IQR), mg	1.98 (0.54 to 5.77)	2.15 (0.65 to 7.00)	.69	1.83 (0.80 to 5.53)	2.91 (0.75 to 5.67)	.25
RASS score at baseline	−3 (−4 to −2)	−3 (−4 to −2)	.53	−3 (−4 to −2)	−3 (−4 to 3)	.11
RASS score during study drug	−0.9 (−1.9 to −0.1)	−1.5 (−2.5 to −0.5)	<.001	−1.0 (−1.9 to −0.2)	−1.7 (−2.5 to −0.7)	<.001
Time at target sedation without rescue medication, % (95% CI)[c]	60.7 (55.4 to 66.1)	56.6 (51.2 to 61.9)	.15	64.6 (60.0 to 69.1)	64.7 (59.9 to 69.4)	.97
Total sedation stops scheduled/ contraindicated/indicated, No. (%)[d]	717/116/601 (83.8)	859/156/703 (81.8)	.32	658/167/491 (74.6)	888/189/699 (78.7)	.07
Sedation stop performed, No. (%)[e]	539 (89.7)	656 (93.3)	.02	437 (89.0)	630 (90.1)	.56
Duration of sedation stop, median (IQR), h[b]	2.4 (1.0 to 6.3)	3.8 (1.5 to 8.4)	.15	1.3 (0.7 to 3.4)	1.0 (0.4 to 3.3)	.07
Spontaneous breathing trial attempted, No. (%)[f]	317 (58.8)	306 (46.6)	<.001	257 (58.8)	324 (51.4)	.02
Contraindications to performing sedation stop, No. (%)[g]						
Severe oxygenation problems	26 (3.6)	40 (4.7)	.38	57 (8.7)	100 (11.3)	.11
Severe cardiovascular instability	21 (2.9)	20 (2.3)	.53	38 (5.8)	28 (3.2)	.02
Need for continuous or deep sedation	56 (7.8)	61 (7.1)	.63	74 (11.2)	69 (7.8)	.02
Previous sedation stop ongoing	30 (4.2)	45 (5.2)	.34	11 (1.7)	14 (1.6)	>.99
Reasons sedation stop not done, No. (%)						
Other clinical indication	29 (4.0)	26 (3.0)	.28	36 (5.5)	44 (5.0)	.65
Procedure/surgery	14 (2.0)	18 (2.1)	.86	15 (2.3)	17 (1.9)	.72
Logistic reason	18 (2.5)	3 (0.3)	<.001	3 (0.5)	8 (0.9)	.37

Abbreviations: IQR, interquartile range; RASS, Richmond Agitation-Sedation Scale.
[a] Exposure calculated from treated patients only and numbers of patients were 247, 250, 246, and 247, respectively; sedation stops were excluded from duration.
[b] Excludes final sedation stop leading to termination of study drug, where numbers of performed sedation stops were for MIDEX, 359 and 460, and PRODEX, 260 and 449, for dexmedetomidine and usual care, respectively. P values for proportional analyses were based on generalized estimating equation model with factors for treatment, time, and country. P values for duration were based on repeated-measures analysis of variance with factors for treatment, time, and country.
[c] Percentage of total time at target sedation.
[d] Scheduled stops was based on duration of study drug exposure. Indicated stops were all occasions where a contraindication was not recorded. Percentage is percentage of number of scheduled sedation stops.
[e] Based on number of indicated stops.
[f] Performed at sedation stop, thus expressed as proportion of sedation stops performed.
[g] More than 1 reason could apply.

ported at similar rates in both groups. First-degree atrioventricular block in MIDEX was observed in 3 patients in each group and, in PRODEX, in 2 propofol patients (0.8%) and 9 dexmedetomidine patients (3.7%) (P=.04). There were no differences between dexmedetomidine and standard care in infectious adverse events. Critical illness polyneuropathy was less common in patients receiving dexmedetomidine than in those receiving propofol (2 patients vs 11 patients, respectively; P=.02). (For detailed adverse and serious adverse events refer to the eAppendix and eTables 12 through 15.)

In the MIDEX trial, rates of neuro-cognitive adverse events through 48 hours of follow-up (agitation, anxiety, delirium, etc) were not different between midazolam and dexmedetomidine patients. In PRODEX, neurocog-nitive adverse events were reported in 71 of 247 propofol patients (29%) and in 45 of 251 dexmedetomidine patients (18%) (P=.008); also, dexmedetomidine patients received concomitant treatment for agitation, anxiety, and delirium less frequently (eTable 15). In both studies, there were no differences between the treatments in number of patients needing reinstitution of sedation due to agitation and anxiety or in delirium assessed using the Confusion Assessment Method for ICU Patients (CAM-ICU)[21] at 48 hours after stopping study sedation. Serious adverse events were equally common between treatment groups in both studies.

COMMENT

These 2 trials demonstrated that dexmedetomidine was not inferior to midazolam or propofol for long-term sedation in mechanically ventilated ICU

Figure 2. Duration of Mechanical Ventilation and Intensive Care Unit Stay
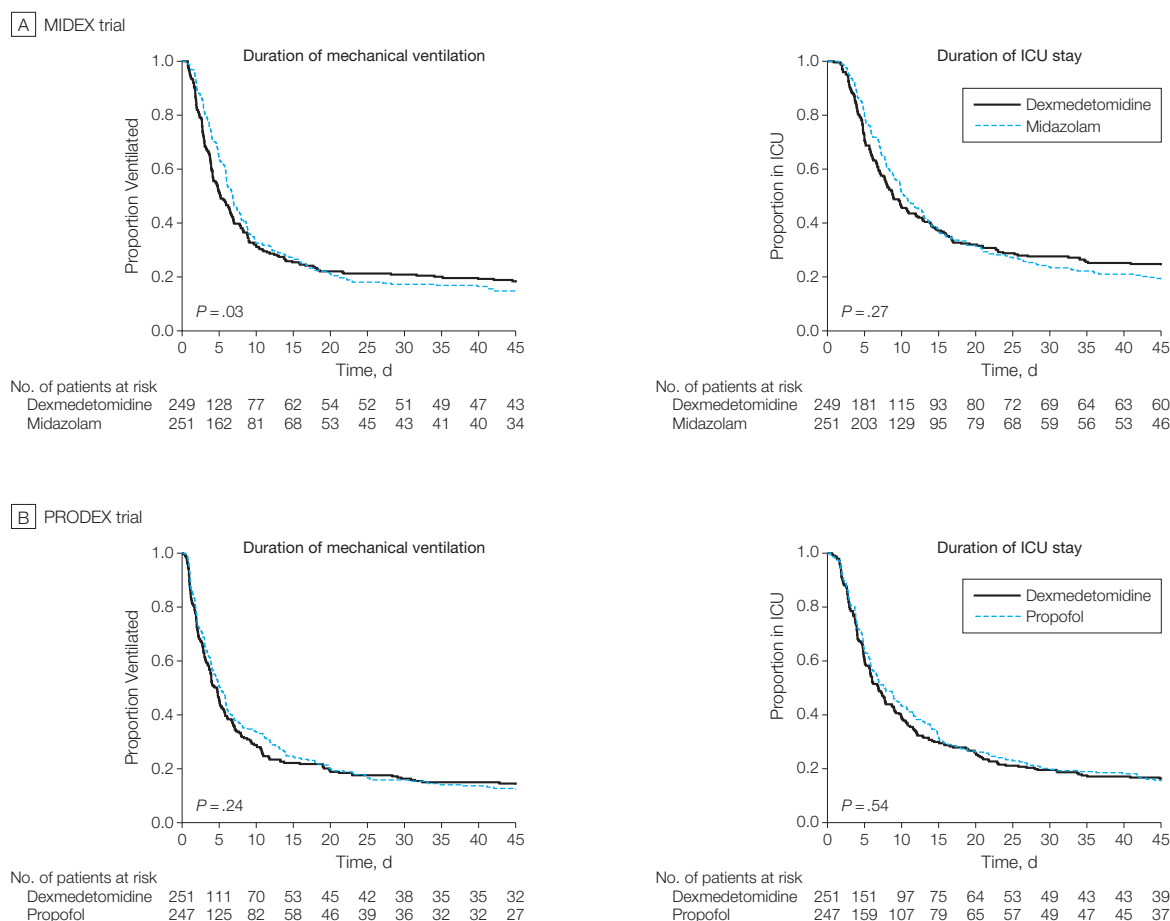
In the MIDEX trial (midazolam vs dexmedetomidine), the median duration of mechanical ventilation was, for dexmedetomidine, 123 hours (interquartile range [IQR], 67-337 hours) and, for midazolam, 164 hours (IQR, 92-380 hours) (Gehan-Wilcoxon P=.03). The median length of stay in the intensive care unit (ICU) from randomization until the patient was medically fit for discharge was, for dexmedetomidine, 211 hours (IQR, 115-831 hours) and, for midazolam, 243 hours (IQR, 140-630 hours; Gehan-Wilcoxon P=.27). In the PRODEX trial (propofol vs dexmedetomidine), the median duration of mechanical ventilation was, for dexmedetomidine, 97 hours (IQR, 45-257 hours) and, for propofol, 118 hours (IQR, 48-327 hours) (Gehan-Wilcoxon P=.24). The median length of stay in the ICU from randomization until the patient was medically fit for discharge was, for dexmedetomidine, 164 hours (IQR, 90-480 hours) and, for propofol, 185 hours (93-520 hours; Cox's proportional hazards test P=.54). Study drugs were given for a maximum of 336 hours in both trials.

Table 3. Patients' Arousability, Ability to Communicate Pain, and Ability to Cooperate With Nursing Care

	Adjusted Mean Estimate (95% CI)			
	Dexmedetomidine	Preferred Usual Care	P Value[a]	Estimate of Difference (95% CI)
Dexmedetomidine vs midazolam (MIDEX)	(n = 249)	(n = 251)		
Total VAS score[b]	49.7 (45.5 to 53.8)	30.0 (25.9 to 34.1)	<.001	19.7 (15.2 to 24.2)
Can the patient communicate pain?	46.3 (41.7 to 50.9)	24.2 (19.7 to 28.8)	<.001	22.1 (17.1 to 27.1)
How arousable is the patient?	58.2 (53.7 to 62.6)	40.7 (36.3 to 45.1)	<.001	17.5 (12.7 to 22.3)
How cooperative is the patient?	44.8 (40.3 to 49.2)	25.1 (20.8 to 29.5)	<.001	19.7 (14.8 to 24.5)
Dexmedetomidine vs propofol (PRODEX)	(n = 251)	(n = 247)		
Total VAS score[b]	51.3 (46.9 to 55.7)	40.1 (35.7 to 44.6)	<.001	11.2 (6.4 to 15.9)
Can the patient communicate pain?	49.3 (44.5 to 54.2)	35.4 (30.5 to 40.4)	<.001	13.9 (8.7 to 19.1)
How arousable is the patient?	59.1 (54.7 to 63.4)	47.8 (43.4 to 52.3)	<.001	11.2 (6.5 to 16.0)
How cooperative is the patient?	47.2 (42.3 to 52.2)	38.0 (33.0 to 43.0)	<.001	9.2 (3.9 to 14.5)

Abbreviation: VAS, visual analogue scale.
[a] Analysis of covariance with effects for treatment, country, and baseline values.
[b] A higher score represents a better outcome.

patients. Dexmedetomidine's noninferiority compared with these standard sedation strategies in mild to moderate sedation was confirmed. Dexmedetomidine appeared to shorten mechanical ventilation compared with midazolam but not compared with propofol; however, time to extubation was reduced compared with both midazolam and propofol. Dexmedetomidine enhanced patients' ability to communicate pain to the nursing staff, possibly contributing to the earlier extubation. Accordingly, dexmedetomidine may provide clinically relevant benefits compared with standard sedation, even when measures to reduce the risks of oversedation are implemented. The better arousability and ability to communicate pain should allow more appropriate use of opioids and facilitate earlier mobilization and functional recovery.

We observed in our pilot study[16] that dexmedetomidine was not suitable for deep sedation. Therefore, these pivotal trials focused on light to moderate sedation. Despite this, the study treatment was discontinued due to lack of efficacy more frequently in dexmedetomidine patients in both trials. With the current maximum dose, lack of efficacy can be expected in approximately 1 in every 8 to 10 patients. Whether higher doses of dexmedetomidine could safely be used should be addressed in future studies. Dexmed-

etomidine doses were substantially lower in the midazolam vs dexmedetomidine than in the propofol vs dexmedetomidine study despite similar sedation levels. This was likely due to the remaining effect of preceding midazolam sedation.

Dexmedetomidine has been proposed to reduce the duration of mechanical ventilation.[16,17] Others observed earlier extubation with dexmedetomidine when compared with midazolam.[17] We observed that the difference between dexmedetomidine and midazolam in the proportion of mechanically ventilated patients changed over time and was not statistically significant in the primary analysis. Because median length of study drug infusion in the midazolam vs dexmedetomidine study was only 42 to 47 hours, any effect of dexmedetomidine would be expected early in a large proportion of patients. Furthermore, since the study drug was limited to 14 days, but mechanical ventilation was considered up to 45 days, standard care given after dexmedetomidine may have reduced any benefit from dexmedetomidine. Also, imputation of length of mechanical ventilation to 45 days in patients who died may have confounded early treatment effects. Accordingly, the alternative statistical analysis indicated significantly shorter mechanical ventilation with dexmedetomidine than midazolam and earlier extubation in

both studies. If only observed data are included, mechanical ventilation is significantly shorter with dexmedetomidine in both trials (eTable 5). The present and previous trials suggest that dexmedetomidine shortens mechanical ventilation compared with benzodiazepine infusions, even when frequent monitoring of sedation and sedation stops are used.

This is the first large-scale study comparing dexmedetomidine with propofol in long-term sedation. Main advantages of propofol are short duration of action and rapid awakening when sedation is stopped,[3,22] unless used longterm in high doses.[13] Mechanical ventilation was shorter with propofol than lorazepam.[22] Our results indicate that duration of mechanical ventilation is similar with dexmedetomidine and propofol, but dexmedetomidine favors earlier extubation.

All sedatives have cardiovascular adverse effects. As an α_2-adrenoreceptor agonist, dexmedetomidine can cause bradycardia and hypotension. As in previous studies,[16,17] bradycardia was more common with dexmedetomidine. Hypotension and cardiovascular instability other than bradycardia rarely necessitated stopping the study in all study groups, despite severe cardiovascular dysfunction (cardiovascular Sequential Organ Failure Assessment score >2) in more than 60% of patients at the baseline. The exclusion of patients with

a specific risk of adverse effects with dexmedetomidine—those with bradycardia and atrioventricular block—may have introduced some bias favoring dexmedetomidine.

The 45-day mortality was higher in the MIDEX study than the PRODEX study ($P=.03$). This was mainly related to the difference in mortality between the groups receiving dexmedetomidine (27.3% in MIDEX vs 17.1% in PRODEX), whereas standard-care group mortalities were comparable (21.1% with midazolam vs 19.4% with propofol). When all dexmedetomidine patients were compared with all standard-care patients, mortality was similar (22.2% vs 20.3%, $P=.49$). This is consistent with the only previous large study comparing dexmedetomidine with midazolam in long-term sedation (30-day mortality, 25% for midazolam vs 23% for dexmedetomidine[17]). The only trial reporting 1-year mortality after dexmedetomidine sedation found no difference between dexmedetomidine and lorazepam.[15]

Delirium is common during prolonged intensive care,[4,7,9,15,17] and sedation may be an independent risk factor.[4] Dexmedetomidine reduced the composite end point of delirium and coma as compared with lorazepam without sedation stops,[15] and delirium as compared with midazolam.[17] Our pilot study suggested increased delirium with dexmedetomidine.[16] In the present studies, incidence of neurocognitive disorders, including delirium, was similar with dexmedetomidine and midazolam, whereas dexmedetomidine was associated with fewer neurocognitive disorders than propofol. Others have found that dexmedetomidine sedation—in contrast to propofol—preserved or even improved cognitive function in patients with decreased baseline cognition.[23] These seemingly conflicting results may be related to the definition of delirium. We used the reported adverse events and assessed delirium using CAM-ICU only once, 48 hours after stopping study drugs. We found more clinically apparent critical illness polyneuromyopathy in propofol patients; this observation is inconclusive and should be studied further.

The main strengths of these studies are the large sample size, proof of noninferiority in maintaining sedation, use of double dummy to avoid unmasking, and frequent sedation assessment and daily sedation stops. There are several limitations. The standard sedation preceding randomization may have masked benefits of dexmedetomidine during shorter exposure. A change of drug may have increased the lack of efficacy early during dexmedetomidine infusion, which was observed in the PRODEX study. Because of clinical contraindications, scheduled sedation stops were not always performed: the rates are similar or slightly higher than those reported by others.[9] Spontaneous breathing trials were performed only in about half of the sedation stops, as compared with approximately 60% of those screened in the Awakening and Breathing Controlled trial.[9] The lack of a usual care control group including bolus administration of midazolam could be considered a study limitation. However, published surveys[24,25] and the usual care in study centers indicate that midazolam infusion is very common. Weaning from mechanical ventilation and criteria for extubation were not standardized. The large sample size and randomization should minimize bias induced by different weaning practices. The effects of the study drugs should be interpreted with the concomitant use of opiates and rescue medications and the target of light to moderate sedation; however, this corresponds to their clinical use. Finally, we assessed sedation from the caregiver's perspective. Future studies should include the patient's perspective of quality of sedation as well.

In summary, dexmedetomidine was noninferior to propofol and midazolam in maintaining the target sedation level in a broad spectrum of ICU patients requiring prolonged mechanical ventilation. Dexmedetomidine appeared to reduce the duration of mechanical ventilation as compared with midazolam, reduced the time to extubation as compared with both midazolam and propofol, reduced delirium as compared with propofol, and was associated with improved patient communication with the nursing staff but had no effect on length of ICU or hospital stay. Incidences of hypotension and bradycardia were higher with dexmedetomidine than with midazolam but comparable with propofol. We conclude that dexmedetomidine is feasible for long-term sedation in intensive care patients and may provide clinically relevant benefits by reducing the duration of invasive ventilation and improving comfort.

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