Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation

Two Randomized Controlled Trials

Sedation in Intensive Care Patients is assumed to reduce discomfort from care interventions, increase tolerance of mechanical ventilation, prevent accidental removal of instrumentation, and reduce metabolic demands during cardiovascular and respiratory instability. Long-term sedation may have serious adverse effects, such as prolonged mechanical ventilation, coma, delirium, delusional memories and post-traumatic stress disorder, impaired cognitive function, prolonged hospitalization, increased costs, and mortality. Daily sedation stops, sedation protocols, spontaneous breathing trials and early mobilization may help reduce these complications.

Current sedatives are problematic in long-term sedation. Benzodiazepines and propofol accumulate unpredictably. High-dose or prolonged propofol use may cause potentially fatal propofol infusion syndrome. Dexmedetomidine, a sedative with high 2-agonist available for ICU sedation, has serious adverse effects. Dexmedetomidine, an α2-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 sedation 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 (measured by Richmond Agitation-Sedation Scale) and superior to control with respect to duration of mechanical ventilation. Secondary end points were patients’ ability to communicate 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 duration of mechanical ventilation appeared shorter with dexmedetomidine (123 hours [IQR, 67-337]) vs midazolam (164 hours [IQR, 92-380]; P=.03) but not with dexmedetomidine (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. Dexmedetomidine 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, dexmedetomidine was not inferior to midazolam and propofol in maintaining light to moderate sedation. Dexmedetomidine reduced duration of mechanical ventilation compared with midazolam and improved patients’ ability to communicate pain compared with midazolam and propofol. More adverse effects were associated with dexmedetomidine.

Trial Registration clinicaltrials.gov Identifiers: NCT00481312, NCT00479661

Context Long-term sedation with midazolam or propofol in intensive care units (ICUs) has serious adverse effects. Dexmedetomidine, an α2-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.

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Conclusions Among ICU patients receiving prolonged mechanical ventilation, dexmedetomidine was not inferior to midazolam and propofol in maintaining light to moderate sedation. Dexmedetomidine reduced duration of mechanical ventilation compared with midazolam and improved patients’ ability to communicate pain compared with midazolam and propofol. More adverse effects were associated with dexmedetomidine.
α₂-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 and—in a pilot study—reduced duration of mechanical ventilation when compared with propofol or midazolam. A multicenter trial in predominantly medical ICU patients found earlier extubation compared with lorazepam and—in a pilot study—reduced duration of mechanical ventilation when compared with midazolam. However, a recent meta-analysis presented inconclusive results for the effect of dexmedetomidine on duration of mechanical ventilation and ICU stay. 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 legal 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) 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 α₂ 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 prepared, 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, 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 bolus 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 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, 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, the intention-to-treat population, the intention-to-treat population, was also performed.

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 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 dexmedetomidine 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],
DEXMEDETOMIDINE FOR LONG-TERM SEDATION

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 = .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**

**MIDEX Trial**
- 249 Randomized to receive dexmedetomidine
  - 188 Completed treatment
  - 60 Treatment withdrawn
  - 23 Lack of efficacy
  - 23 Adverse or serious adverse event
  - 2 Protocol violation
  - 16 Other reasons
- 251 Included in intention-to-treat analysis
  - 187 Included in per-protocol analysis
  - 2 Excluded
  - 8 Missing inclusion criteria
  - 8 Incorrect dosing
  - 1 Received excluded medication
  - 5 Missing assessments
- 15 324 Patients assessed for eligibility
- 8301 Receiving mechanical ventilation
- 7800 Excluded
  - 7642 Did not meet inclusion criteria
  - 1822 Not expected to need moderate sedation
  - 529 Not prescribed light to moderate sedation
  - 1486 Other reasons
  - 2418 Acute severe neurological disorder
  - 1896 Had any other exclusion criterion
  - 133 Declined to participate
  - 25 Other reasons

**PRODEX Trial**
- 251 Randomized to receive dexmedetomidine
  - 180 Completed treatment
  - 71 Treatment withdrawn
  - 36 Lack of efficacy
  - 29 Adverse or serious adverse event
  - 1 Nonpharmacological intervention
  - 1 Protocol violation
  - 7 Other reasons
- 251 Included in intention-to-treat analysis
  - 223 Included in per-protocol analysis
  - 28 Excluded
  - 3 Missing inclusion criteria
  - 1 Met exclusion criteria
  - 7 Incorrect dosing
  - 1 Received excluded medication
  - 10 Missing assessments
- 19 251 Patients assessed for eligibility
- 11 1610 Receiving mechanical ventilation
- 11 110 Excluded
  - 10 841 Did not meet inclusion criteria
  - 12 462 Not expected to need moderate sedation
  - 11 72 Not prescribed light to moderate sedation
  - 1370 Other reasons
  - 2688 Acute severe neurological disorder
  - 2367 Had any other exclusion criterion
  - 251 Declined to participate
  - 18 Other reasons

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

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine vs Midazolam Study (MIDEX)</th>
<th>Dexmedetomidine vs Propofol Study (PRODEX)</th>
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<tbody>
<tr>
<td></td>
<td>Median (IQR) n = 249</td>
<td>Median (IQR) n = 251</td>
</tr>
<tr>
<td>Main reason for admission to ICU, No. (%)</td>
<td>182 (73.1) 171 (68.1)</td>
<td>182 (71.0) 181 (69.3)</td>
</tr>
<tr>
<td>Organ failures (SOFA score &gt;2), No. (%)</td>
<td>149 (59.8) 154 (61.4)</td>
<td>151 (60.2) 151 (61.3)</td>
</tr>
<tr>
<td>Total SOFA score, Median (IQR)</td>
<td>7.0 (5.0-9.0) 7.0 (5.0-9.0)</td>
<td>7.0 (5.0-9.0) 7.0 (5.0-9.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

Table 2. Details of Study Drug Administered and Sedation Stops

<table>
<thead>
<tr>
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<tr>
<td></td>
<td>Median (IQR) n = 249</td>
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</tr>
<tr>
<td>Study drug treatment, median (IQR)</td>
<td>42 (23 to 72) 43 (24 to 92)</td>
<td>42 (22 to 72) 47 (25 to 103)</td>
</tr>
<tr>
<td>Dose of study drug, µg/kg/h or mg/kg/h</td>
<td>0.450 (0.273 to 0.756) 0.062 (0.041 to 0.098)</td>
<td>0.925 (0.673 to 1.170) 1.752 (1.211 to 2.424)</td>
</tr>
<tr>
<td>Patients receiving rescue sedation, No. (%)</td>
<td>102 (43.8) 114 (45.4)</td>
<td>182 (72.5) 159 (64.4)</td>
</tr>
<tr>
<td>Total dose of rescue sedation, median (IQR), mg</td>
<td>195 (50 to 440) 210 (60 to 300)</td>
<td>17 (6.0 to 41.0) 14 (6.0 to 28.5)</td>
</tr>
<tr>
<td>Patients receiving fentanyl, No. (%)</td>
<td>190 207</td>
<td>194 194</td>
</tr>
<tr>
<td>RASS score at baseline</td>
<td>–3 (–4 to –2) –3 (–4 to –2)</td>
<td>–3 (–4 to –2) –3 (–4 to –2)</td>
</tr>
<tr>
<td>RASS score during study drug</td>
<td>–0.9 (–1.9 to –0.1) –1.5 (–2.5 to –0.5)</td>
<td>–1.0 (–1.9 to –0.2) –1.7 (–2.5 to –0.7)</td>
</tr>
<tr>
<td>Time at target sedation without rescue medication, % (IQR)</td>
<td>60.7 (55.4 to 66.1) 56.6 (51.2 to 61.9)</td>
<td>64.6 (60.0 to 69.1) 64.7 (69.9 to 69.4)</td>
</tr>
<tr>
<td>Total sedation stops scheduled/contraindicated/indicated, No. (%)</td>
<td>717/116/601 (83.8) 859/156/703 (81.8)</td>
<td>665/167/490 (74.8) 889/198/699 (78.7)</td>
</tr>
<tr>
<td>Sedation stop performed, No. (%)</td>
<td>539 (87.7) 656 (63.3)</td>
<td>437 (89.9) 630 (90.1)</td>
</tr>
<tr>
<td>Duration of sedation stop, median (IQR), h</td>
<td>2.4 (1.0 to 6.3) 3.8 (1.5 to 8.4)</td>
<td>1.3 (0.7 to 3.4) 1.0 (0.4 to 3.4)</td>
</tr>
<tr>
<td>Spontaneous breathing trial attempted, No. (%)</td>
<td>317 (58.8) 306 (64.6)</td>
<td>257 (58.8) 324 (61.4)</td>
</tr>
<tr>
<td>Contraindications to performing sedation stop, No. (%)</td>
<td>26 (3.6) 40 (4.7)</td>
<td>57 (8.7) 100 (11.3)</td>
</tr>
<tr>
<td>Severe oxygenation problems</td>
<td>21 (2.9) 20 (2.4)</td>
<td>38 (5.8) 28 (3.0)</td>
</tr>
<tr>
<td>Severe cardiovascular instability</td>
<td>56 (7.8) 61 (7.1)</td>
<td>74 (11.4) 69 (7.8)</td>
</tr>
<tr>
<td>Need for continuous or deep sedation</td>
<td>30 (4.2) 45 (5.2)</td>
<td>34 (11.7) 14 (11.6)</td>
</tr>
<tr>
<td>Previous sedation stop ongoing</td>
<td>29 (4.0) 26 (3.9)</td>
<td>28 (5.5) 44 (5.0)</td>
</tr>
<tr>
<td>Other clinical indication</td>
<td>14 (2.0) 18 (2.1)</td>
<td>19 (2.7) 17 (1.9)</td>
</tr>
<tr>
<td>Logistic reason</td>
<td>18 (2.5) 3 (0.5)</td>
<td>3 (0.5) 8 (0.9)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; RASS, Richmond Agitation-Sedation Scale.

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ported at similar rates in both groups. First-degree atrioventricular block in MIDE 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 MIDE trial, rates of neurocognitive adverse events through 48 hours of follow-up (agitation, anxiety, delirium, etc) were not different between midazolam and dexmedetomidine patients. In PRODEX, neurocognitive 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)\(^2\) 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

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**Figure 2. Duration of Mechanical Ventilation and Intensive Care Unit Stay**

In the MIDE 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) \((P = .03)\). 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, 49-257 hours) and, for propofol, 118 hours (IQR, 48-327 hours) \((P = .44)\). 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.
Dexmedetomidine could safely be used should higher doses of dexmedetomidine 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 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. Dexmedetomidine 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.\textsuperscript{16,17} Others observed earlier extubation with dexmedetomidine when compared with midazolam.\textsuperscript{11} 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,\textsuperscript{3,22} unless used long-term in high doses.\textsuperscript{13} Mechanical ventilation was shorter with propofol than lorazepam.\textsuperscript{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 \(\alpha_2\)-adrenoceptor agonist, dexmedetomidine can cause bradycardia and hypotension. As in previous studies,\textsuperscript{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

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

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

Abbreviation: VAS, visual analogue scale.\textsuperscript{a}Analysis of covariance with effects for treatment, country, and baseline values.\textsuperscript{b}A higher score represents a better outcome.
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). The only trial reporting 1-year mortality after dexmedetomidine sedation found no difference between dexmedetomidine and lorazepam.

Delirium is common during prolonged intensive care and sedation may be an independent risk factor. Dexmedetomidine reduced the composite end point of delirium and coma as compared with lorazepam without sedation stops, and delirium as compared with midazolam. Our pilot study suggested increased delirium with dexmedetomidine. 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. 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. 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. The lack of a usual care control group including bolus administration of midazolam could be considered a study limitation. However, published surveys and the usual care in study centers indicate that midazolam infusion is 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, 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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Conflict of Interest Disclosures: Drs Jakob and Ruokonen contributed equally as first authors. Drs Ruokonen, Jakob, and Takala had full access to the study data. Dr Takala had the final responsibility for the decision to submit the manuscript. Drs Jakob and Ruokonen served as co–principal investigators and, with Dr Takala, conceived the original idea of the 2 studies. Study concept and design: Jakob, Ruokonen, Grounds, Sarapohja, Garratt, Pocock, Bratty, Takala. Drafting of the manuscript: Jakob, Ruokonen, Grounds, Sarapohja, Garratt, Pocock, Bratty, Takala. Critical revision of the manuscript for important intellectual content: Jakob, Ruokonen, Grounds, Sarapohja, Garratt, Pocock, Bratty, Takala. Statistical analysis: Jakob, Ruokonen, Sarapohja, Pocock, Takala. Obtained funding: Jakob, Takala. Administrative, technical, or material support: Ruokonen, Sarapohja, Garratt, Bratty. Study supervision: Jakob, Ruokonen, Takala.

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the regulatory filing of the drug; the money was also paid into a departmental fund. Additionaly, Drs Jakob, Ruegg and Karla also had full access to the data and performed the analyses independently from those of the sponsor. The results reported from these independent analyses were identical to those presented by the MIDEX Study Group Members.

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Independent Statistical Analysis: Analysis was under- taken by Dr Duolao Wang (Medical Statistics Dep- artment, London School of Hygiene and Tropical Medicine, London, United Kingdom) under the super- vision of Dr Pocock, Medical Statistics Depart- ment, London School of Hygiene and Tropical Medi- cine. Full access to all of the data used in the study was provided and an independent analysis of the pri- mary and secondary end points reported in this ar- ticle was performed by repeating the analyses and veri- fy ing P values and 95% confidence intervals. Conclusions were based on the results of the statistical analysis and a review of the draft manuscript. All authors had full access to the data and interpreted the results. Any disagreements were resolved by the senior author.

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