Critical Review Form
Therapy

PGY-1

Jakob SM, Ruokonen E, Grounds RM, et al; Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012 Mar 21;307(11):1151-60.

Objectives: **To assess "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." (p. 1152)**

Methods: **This article reports the results of two multicenter, randomized, double-blind controlled trials conducted from 2007 to 2010. The MIDEX trial was conducted at 44 centers in 9 European countries and the PRODEX trial was conducted at 31 centers in 6 European countries and two in Russia. Inclusion criteria for both studies were age ≥ 18, need for invasive mechanical ventilation, need for light to moderate sedation (RASS score 0 to -3), planned use of midazolam or propofol for at least 24 hours following randomization, and ability to randomize the patient within 72 hours of ICU admission and within 48 hours of initiating continuous sedation. Exclusion criteria were acute severe neurologic disorder, mean arterial pressure < 55 mmHg despite appropriate hydration and vasopressor use, heart rate < 50, grade II or III AV conduction block, or use of α_2 agonists of antagonists within the previous 24 hours.**

Patients were randomized in a 1:1 fashion to either current standard sedation medication (propofol or midazolam depending on treatment site) or dexmedetomidine. Treatments were administered in a double-dummy design, with normal saline as the dummy treatment. Drugs were titrated by the nurses to maintain a targeted RASS. All patients were followed for 45 days.

The primary efficacy outcome was the proportion of time in target sedation range (RASS 0 to -3) without using rescue therapy. The secondary efficacy outcome was duration of mechanical ventilation. Other outcomes included length of ICU stay and nurse's assessment of arousal, ability to cooperate with care, and ability to communicate pain.

A total of 500 patients were enrolled in the MIDEX trial (249 randomized to dexmedetomidine and 251 to midazolam) and 498 patients were enrolled in the PRODEX trial (251 randomized to dexmedetomidine and 247 to propofol). In the MIDEX trial, 53 midazolam patients (21.1%) and 68 dexmedetomidine patients (27.3%) died prior to follow-up; in the PRODEX trial, 48 propofol patients (19.4%) and 43 dexmedetomidine patients (17.1%) died prior to follow-up.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Randomization occurred in a 1:1 fashion, stratified by study center in blocks of four.
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "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." (p. 1152). This should be sufficient to prevent subversion of the randomization process.
3.	Were patients analyzed in the groups to which they were randomized?	No. For the primary outcome (proportion of time in the target sedation range), the authors looked at the per-protocol population "to avoid bias toward noninferiority." (p. 1153) A secondary intention to treat analysis was also conducted for this outcome. All other outcomes were assessed using intention to treat analyses.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Mostly yes. In the MIDEX trial, patients in the dexmedetomidine group were somewhat more likely to be male than those in the midazolam group (61.4% vs. 69.7%). Otherwise, patients in both studies were similar with respect to age, reason for admission (medical vs. surgical vs. trauma), infection at ICU admission, rates of failure of specific organs/systems, and overall SOFA score. The authors do not report rates of need for vasopressors, degree of hypoxemia, or vital signs.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. Besides the patients being intubated and hence mostly unaware of treatment, investigators also used a double-dummy

		design (using normal saline as the dummy), effectively blinding patients and clinicians. "Propofol and propofol dummy were prepared, connected, and removed by independent personnel and infused with nontransparent black syringes, infusion tubings, and connectors." (p. 1152)
2.	Were clinicians aware of group allocation?	No. As stated above, investigators used a double-dummy design (using normal saline as the dummy), effectively blinding patients and clinicians.
3.	Were outcome assessors aware of group allocation?	Presumably yes. Though not specifically mentioned, it is presumed that outcome assessors would also not be aware of group allocation.
4.	Was follow-up complete?	Yes. Only 4 total patients in the PRODEX trial (3 in the dexmedetomidine group and 1 in the propofol group) were lost to follow-up (0.8%). No patients in the MIDEX trial were lost to follow-up.
II.	**What are the results ?**	

1.	How large was the treatment effect?	• For the primary efficacy outcome, proportion of time spent at target sedation without need for rescue meds was similar between the two groups in both studies:
		  ○ Midazolam - 56.6%, dexmedetomidine - 60.7%; ratio 1.07 (95% CI 0.97-1.18).
		  ○ Propofol - 64.7%, dexmedetomidine - 64.6%; ratio 1.00 (95% CI 0.92-1.08).
		• Dexmedetomidine patients had higher RASS scores in both studies.
		• Discontinuation of study drug due to lack of efficacy was more common in dexmedetomidine patients compared to midazolam patients (9% vs. 4%, $p = 0.02$) and compared to propofol patients (14% vs. 5%, $p < 0.001$).
		• The median duration of mechanical ventilation was shorter in dexmedetomidine patients compared to midazolam patients (123 hours vs. 164 hours, $p = 0.03$), but did not differ significantly from propofol patients (97 hours vs. 118 hours, $p = 0.24$).

		• The median ICU length of stay did not differ significantly in either study. • Hypotension occurred more frequently in dexmedetomidine patients compared with midazolam patients (20.6% vs. 11.6%, p = 0.007), as did bradycardia (14.2% vs. 5.2%, p < 0.001). These adverse events occurred at similar rates in dexmedetomidine and propofol patients.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Presumably yes. Although both studies were conducted in Europe, these were critically ill, intubated patients in the ICU, and their physiology should not be different from a similar cohort in the US.
2.	Were all clinically important outcomes considered?	No. While the authors considered the proportion of time spent at target sedation level, duration of mechanical ventilation, rates of medication discontinuation due to lack of efficacy, and other important outcomes, they did not address rates of delirium, ICU psychosis, or patient satisfaction. Cost of care was also not evaluated.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study suggest noninferiority of dexmedetomidine compared to midazolam and propofol with respect to proportion of time spent at target sedation, as well as a shorter duration of mechanical ventilation compared to midazolam, discontinuation of study drug due to lack of efficacy was more common in dexmedetomidine patients in both studies. Given that one of the primary reported benefits of dexmedetomidine is more rapid offset with decreased risk of delirium, we would expect to see a much shorter duration of mechanical ventilation in both group. Additionally, rates of delirium following extubation were not studied. While dexmedetomidine seems safe and reasonable, these two studies do not confirm a significant benefit over the two alternatives.

Limitations:

1. **Despite patients receiving dexmedetomidine reportedly having a similar proportion of time at desired level of sedation in both studies, patients receiving midazolam and propofol achieved deeper sedation, and dexmedetomidine was more likely to be ineffective, requiring discontinuation in 1 of every 8-10 patients.**

2. **Dexmedetomidine doses were much lower in MIDEX than PRODEX, despite the same desired level of sedation, which likely impacted efficacy measures.**

3. **Mechanical ventilation weaning and extubation criteria not standardized (external validity).**

4. **One of the most touted benefits of dexmedetomidine is a reduction in delirium, which was not measured in this study.**

5. **Patient-centered outcomes (reductions in morbidity and mortality) were not assessed, and neither was cost of care.**

Bottom Line:

These two blinded, randomized controlled trials comparing dexmedetomidine with midazolam and propofol demonstrated noninferiority of dexmedetomidine with regards to the proportion of time spent at the desired level of sedation, with a decreased in duration of mechanical ventilation compared to midazolam, but no difference compared to propofol. Imbalances in dosing, resulting in lower levels of sedation among patients receiving dexmedetomidine compared to the standard drugs, and lack of objective criteria for weaning of mechanical ventilation and extubation suggest that there may be issues with both internal and external validity. Additionally, patient-centered outcomes and cost were not assessed in this study, nor was the incidence or degree of delirium.