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Weighing the costs and benefits of a sedative

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Critically ill patients traditionally received heavy sedation 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 the patient, protocols to target sedation to a pre-specified level, emphasis on analgesia first, and a change from default sedation for mechanically ventilated patients to individual assessment of need.[4]

In 1999, dexmedetomidine was introduced in the United States market as a new sedative for use in mechanically ventilated patients for up to 24 hours. Common sedatives, such as propofol and benzodiazepines, act on the GABA receptor and produce dose-dependent respiratory depression along with sedation. Dexmedetomidine is a highly selective alpha-2 agonist (closely related to clonidine) with the potential advantages of anxiolysis and some analgesia *without* respiratory depression or amnesia.[5] Studies comparing dexmedetomidine to benzodiazepines for longer term (i.e. 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 alpha-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 receiving continuous sedation.[8]

Why has dexmedetomidine not been embraced with greater enthusiasm in the US? For many, a 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 $1,166 for dexmedetomidine versus $60 for midazolam in one study).[9] Second, the documented benefits versus benzodiazepines are short-term and have not (yet) been translated into tangible long-term outcomes for patients.[6, 7] And a final barrier may be a lack of information relevant to clinicians; prior large trials have only compared dexmedetomidine to benzodiazepines, but many clinicians use propofol in preference to benzodiazepines for sedation of general ICU patients.[10, 11]

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In this issue of *JAMA*, Jakob et al[12] provide data from a large, multicenter randomized controlled trial (RCT) comparing dexmedetomidine with propofol (PRODEX), paired with a "twin" study of dexmedetomidine versus midazolam (MIDEX). The combined studies involved 1,000 patients in 75 ICUs mostly in Europe. The design of the parallel RCTs assigned each ICU to use either midazolam or propofol for the control arm based on the usual institutional practice – a great solution to decrease the likelihood that controls would receive anything other than "usual" care.

Both studies had two primary objectives. The first was to test the non-inferiority of dexmedetomidine with regard to the ability to achieve a chosen level of sedation. The outcome was time spent at a target sedation level using the Richmond Agitation Sedation Scale (RASS).[13] The target chosen was broad: -3 (movement or eye opening to voice, but no eye contact) to zero (alert and calm). This target was successfully met in the two 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 non-invasive). Other outcomes measured included time to extubation (until removal of endotracheal tube), and lengths 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 non-invasive ventilation, and/or imputation of data missing or for patients who died. 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] These new trials did not provide standardized assessments of delirium. But 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 no matter how well designed. Any single study can only examine one approach to using a medication, in this case taking patients off 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 uni-dimensional 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 incidents, and neurocognitive events requiring treatment.

Blinding is also a challenge. Some aspects of blinding sedation studies are purely practical: for example, propofol is in a lipid emulsion, and even a single drop out of the end of the IV tubing will reveal the identity of the medication. PRODEX 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. The 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 mis-match in the dosing.[16] In attempting to choose equivalent doses, blinded studies to date have often paired relatively low doses of dexmedetomidine with doses of benzodiazepines/propofol that seem likely to cause a deeper level of sedation, as occurred in both of these control groups.[12]

Finally, 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] Alternative, 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 (versus 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 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 may be attributable to the fact that the majority of these patients only require short-term mechanical ventilation, which allows clinicians to use dexmedetomidine in line with FDA guidelines. But this choice may also make economic sense since 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 two RCTs provide important evidence that dexmedetomidine is an effective sedative compared with both midazolam and propofol, and its use is 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 US 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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References

1. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000; 342(20):1471–1477. [PubMed: 10816184]
2. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009; 373(9678):1874–1882. [PubMed: 19446324]
3. Girard T, Pandharipande P, Ely EW. Delirium in the intensive care unit. Critical Care. 2008; 12(Suppl 3):S3. [PubMed: 18495054]
4. Riker RR, Fraser GL. Altering intensive care sedation paradigms to improve patient outcomes. Crit Care Clin. Jul; 2009 25(3):527–538. [PubMed: 19576528]
5. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. Anesthesiology. 1992; 77(6):1125–1133. [PubMed: 1361310]
6. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA. 2007; 298(22):2644–2653. [PubMed: 18073360]
7. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009; 301(5):489–499. [PubMed: 19188334]
8. Wunsch H, Kahn JM, Kramer AA, et al. Dexmedetomidine in the care of critically ill patients from 2001 to 2007: an observational cohort study. Anesthesiology. 2010; 113(2):386–394. [PubMed: 20613466]
9. Dasta JF, Kane-Gill SL, Pencina M, et al. A cost-minimization analysis of dexmedetomidine compared with midazolam for long-term sedation in the intensive care unit. Crit Care Med. Feb; 2010 38(2):497–503. [PubMed: 19789442]
10. Wunsch H, Kahn JM, Kramer AA, Rubenfeld GD. Use of intravenous infusion sedation among mechanically ventilated patients in the United States. Crit Care Med. 37(12):3031–3039. [PubMed: 19633543]
11. Egerod I, Christensen BV, Johansen L. Trends in sedation practices in Danish intensive care units in 2003: a national survey. Intensive Care Med. Jan; 2006 32(1):60–66. [PubMed: 16283160]
12. Jakob S. Dexmedetomidine vs. Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation: Two Randomized Controlled Trials. JAMA. 2012
13. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002; 166(10):1338–1344. [PubMed: 12421743]
14. Reade MC, O'Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. Crit Care. 2009; 13(3):R75. [PubMed: 19454032]
15. Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of Delirium with Dexmedetomidine Compared with Morphine Based Therapy after Cardiac Surgery: A Randomized Controlled Trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). Anesthesiology. 2009; 111(5): 1075–1084. [PubMed: 19786862]
16. Wunsch H, Meltzer JS. Sedation with dexmedetomidine vs lorazepam in mechanically ventilated patients. JAMA. Apr 2; 2008 299(13):1540–1541. [PubMed: 18387926]
17. Angus DC, Carlet J. Surviving intensive care: a report from the 2002 Brussels Roundtable. Intensive Care Med. 2003; 29(3):368–377. [PubMed: 12536269]
18. Kahn JM, Rubenfeld G, Rohrbach J, Fuchs B. Cost Savings Attributable to Reductions in Intensive Care Unit Length of Stay for Mechanically Ventilated Patients. Medical Care. 2008; 46(12):1126–1233.