Critical Review Form
Therapy

PGY-4

Tanaka LM, Azevedo LC, Park M, et al; ERICC study investigators.. Early sedation and clinical outcomes of mechanically ventilated patients: a prospective multicenter cohort study. Crit Care. 2014 Jul 21;18(4):R156.

Objectives: **"To describe the association of early sedation strategies (sedation depth and sedative choice) with clinical outcomes of mechanically ventilated adult ICU patients, with hospital mortality as the primary outcomes." (p. 2)**

Methods: **This retrospective study involved a secondary analysis of prospectively collected data from the multicenter Brazilian Research in Intensive Care Network (BRICNet), conducted at 45 Brazilian ICUs. Adults patients (18 years or older) requiring invasive mechanical ventilation during the first 48 hours of ICU admission and receiving sedative agents on day 2 of mechanical ventilation were eligible for inclusion. Exclusion criteria included primary neurologic disorders, use of noninvasive mechanical ventilation only, and missing data regarding sedation depth on the second day of mechanical ventilation.**

The Glasgow Coma Scale (GCS), originally reported as part of the Sequential Organ Failure Assessment (SOFA) score, was used as a surrogate marker of sedation depth, with a score of < 9 representing deep sedation a score ≤ 9 representing light sedation. Patients were analyzed according to the depth of sedation documented on the second day of mechanical ventilation.

Between June 1, 2011 and July 31, 2011, 773 patients were enrolled in the BRICNet, of whom 373 met inclusion criteria. An additional 51 patients were missing data regarding sedation depth at day 2, leaving 322 patients in the final analysis. The overall median age was 59 and 58% were male. Overall ICU mortality was 30.4% and hospital mortality was 38.8%. Deep sedation was observed in 113 patients (35.1%), while light sedation was observed in 209 patients (64.9%).

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	No. This was a retrospective study in which patients were analyzed according to the depth of sedation documented on the second day of mechanical ventilation. No attempt was made

		to control for any potential confounders.
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?	N/A. This study was not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	N/A. Patients were analyzed purely based on the level of sedation documented on day two of mechanical ventilation, regardless of the desired level of sedation.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Patients in the deep sedation group were more likely to be male (70% vs. 52%), had lower scores on the Charlson Comorbidity Index, and had higher admission SAPS3 and SOFA scores. The cause of respiratory failure was similar between the groups.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. Patients were intubated and sedated, and hence would not be aware of any treatments administered or the level of sedation.
2.	Were clinicians aware of group allocation?	Yes. Clinicians would have been aware of sedatives administered and level of sedation achieved, but as this was a retrospective study using previously collected data, clinicians would not have been aware of the parameters being studied. It seems unlikely that performance bias would have affected the outcomes.
3.	Were outcome assessors aware of group allocation?	Yes. The authors make no mention of outcome assessors or data collectors being blinded. As the outcomes were all fairly objective, it seems unlikely that observer bias would have had an affect on the study results.
4.	Was follow-up complete?	Yes. All outcomes were measured during the hospitalization, and hence outcome data was available for all included patients.
II.	**What are the results?**	
1.	How large was the treatment effect?	• Patients in the deep sedation group had a longer duration of ventilation compared to those in the light sedation group (median 7 days vs. 5 days, p = 0.041) and were more likely to receive a tracheostomy (38.9% vs. 22%, p = 0.001). • There was a trend toward higher ICU

		mortality (37.2% vs. 26.8%; RR 1.4, 95% CI 1.0 to 1.9) and hospital mortality (46% vs. 34.9%; RR 1.3, 95% CI 1.0 to 1.7) in the deep sedation group. • In logistic regression, deep sedation was reportedly an independent predictor of increased hospital mortality, with an OR of 2.36 (95% CI 1.31 to 4.25).
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?	Likely yes. These were ventilated patients in the ICU at any of several hospitals in Brazil. While there may be some differences in the presence of comorbidities and in care provided, it seems likely that illness severity and outcomes would be similar to those seen in our institution.
2.	Were all clinically important outcomes considered?	No. The authors looked at short-term, in-hospital outcomes, and did not address cost or quality of life issues. They also did not address hospital length of stay, ICU-free days, or ventilator-free days.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This study was a retrospective look at previously collected data, and was neither designed to nor capable of looking at causation. The association between deep sedation and worse outcomes may reflect the higher illness severity observed in that group of patients, and may not indicate a true "treatment effect." It is therefore not possible to make any conclusions regarding the harm or benefit of a certain sedation strategy.

Limitations:

1. **GCS, rather than the classically used Richmond Agitation-Sedation Scale (RASS), was used as a surrogate marker for sedation depth due to availability of this information in the database. The study reported to justify this (Ely 2003) actually demonstrated poor interrater reliability for GCS in intubated patients (weighted kappa 0.64).**

2. **No *a priori* primary outcome was identified.**

3. **This was a retrospective study in which patients were analyzed according to the depth of sedation documented on the second day of mechanical ventilation, regardless of the desired level of sedation or means of sedation. It is likely that in some cases the level of sedation was a result of the patient's disease process, rather than any treatment provided by the clinicians.**

4. **No attempt to control for known confounders, hence the study was unable to determine if the effect size was due to association versus causation.**

Bottom Line:

This retrospective study conducted using date from a previously collected database demonstrated longer duration of ventilation among patients with deep vs. light sedation (median 7 days vs. 5 days, p = 0.041), higher tracheostomy rates (38.9% vs. 22%, p = 0.001), and a trend toward higher ICU mortality (RR 1.4, 95% CI 1.0 to 1.9) and hospital mortality (RR 1.3, 95% CI 1.0 to 1.7). The retrospective nature of this study and lack of balance between groups make it more likely that these differences were due to an association rather than causation, with sicker patients either receiving deeper sedation or being more sedated due to their disease processes. It is impossible to draw any clinically meaningful conclusions from these results.