

RESEARCH NEWS

Sedatives in patients who were mechanically ventilated: between a rock and a hard place?

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Associations between different sedatives and ventilator-associated events, length of stay, and mortality in patients who were mechanically ventilated. Published in *Chest*, June 2016.^[1]

Why was this research done?

The management of pain, agitation, anxiety and delirium in mechanically ventilated patients on the intensive care unit has been a clinical challenge for years. Previous research has shown that drug choice as well as methods of administering and titrating the medication affect patient outcomes. Current practice guidelines recommend lighter levels of sedation and the preferential use of non-benzodiazepines such as propofol or dexmedetomidine.^[2]

However, until now, it is not known whether there are important differences between propofol and dexmedetomidine compared with benzodiazepines or compared with one another. Furthermore, implementing findings from selected patient cohorts in randomised controlled trials into daily practice in the general population admitted to the intensive care unit can be difficult.

This study evaluates a large, diverse cohort of unselected patients and compares the effects of different sedative agents on hazards for ventilator-associated events (VAE), extubation, hospital discharge and hospital mortality.

How was this investigated?

In this single-centre retrospective study, 9603 episodes of mechanical ventilation lasting ≥ 3 calendar days between 2006 and 2013 were identified. Daily exposure to benzodiazepines, propofol and dexmedetomidine was registered. Proportional sub-distribution hazards models were created with competing risks to estimate the impact that exposure to each of these agents has on VAEs, time to extubation, time to hospital discharge, and death. Hazard ratios were calculated as the effect of receiving the medication of interest versus a

comparator during each of the 3 days prior to VAE onset or extubation, plus 1 extra day in the period from intubation until 4 days prior to the outcome of interest.

All models were adjusted for severity of illness by calculating each patient's predicted probability of death at the time of initiation of mechanical ventilation by using a score optimised for this dataset.

The authors adjusted for additional clinical factors that may have influenced choices of sedatives and outcomes. Furthermore, two sensitivity analyses were conducted to test the robustness of the findings: patients undergoing cardiac and noncardiac surgery were analysed separately, and an analysis restricted to patients managed almost exclusively with one type of sedative was performed.

Main findings

Approximately 66% of patients received at least 1 day of benzodiazepines, 62% received at least 1 day of propofol and 12% received at least 1 day of dexmedetomidine. The agents were often used concurrently.

Benzodiazepines and propofol were both associated with increased hazards for VAEs compared with regimens without these agents (1.4 [95% CI 1.1-1.7] and 1.3 [95% CI 1.1-1.6]). In contrast, dexmedetomidine was not associated with increased risk for VAEs compared with other regimens. There were no differences between benzodiazepines versus propofol in hazards for VAEs. A trend towards fewer VAEs was seen with dexmedetomidine versus benzodiazepines and with dexmedetomidine versus propofol. However, this was not significant.

Regarding time to extubation, there was a lower hazard ratio for benzodiazepines (0.89; 95% CI 0.83-0.96; $p=0.002$) suggesting a decreased daily probability of extubation, where propofol was associated with an increased hazard ratio (1.2; 95% CI 1.1-1.3; $p<0.0001$), suggesting a decreased time to

extubation. Dexmedetomidine was associated with higher hazards for extubation compared with benzodiazepines and propofol. There were no significant differences regarding hospital discharge and death.

Consequences for daily practice

The outcome of this large observational study probably reflects the experience of many clinicians regarding the use of different sedatives and their effects; however, although non-benzodiazepines and specifically dexmedetomidine were associated with less VAEs and a shorter time to extubation this should be interpreted with caution.

First of all there were relatively few patients receiving dexmedetomidine, suggesting a selection bias. This might have been due to a time bias, as dexmedetomidine was relatively new and probably used less in the first few years of the study. Furthermore sedation and time to extubation matters in itself changed during the study period, also accounting for a time bias. Confounders such as for example drug abuse in the previous

history were not reported. All data were extracted from charts and might not have been complete.

Furthermore, there were no dosages reported nor sedative levels. Therefore it remains unclear what drove the results of this study. Were the outcomes reflected by the drug used or the sedative effect? This question is still not answered and warrants further study in other designs.

Disclosures

The author declares no conflict of interest. No funding or financial support was received.

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