Reviewer
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Early Sedation with Dexmedetomidine in Critically Ill Patients.
Shehabi Y, Howe BD, Bellomo R, Arabi YM, et al, for the ANZICS Clinical Trials Group and the SPICE III Investigators. N Eng J Med 2019 Jun 27;380(26);2506-2517.

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Context
This article investigates the effect of using dexmedetomidine ("Dex") alone or as the primary sedative agent for mechanically ventilated ICU patients. This study adds to previous literature comparing Dex to benzodiazepines and/or propofol showing a benefit of Dex with respect to decreased ventilator days and incidence of delirium[1-3], and non-inferiority to propofol for achievement of light sedation[1]. The theoretical advantage of Dex for sedation is the preservation of a level of arousability that may allow interaction with patients, neurological exams, and even ventilator weaning and extubation with the medication still infusing to reduce discomfort or agitation. It also provides some analgesia as well as sedation. Some prior studies on Dex were supported by, or performed in conjunction with, pharmaceutical companies. While the study drug used in this study was supplied by pharmaceutical companies, no other funding by those companies was declared and according to the manuscript they had no role in the design, analysis, or reporting of this trial.

Methods
- Open-label randomized study, assigning patients in a 1:1 ratio to receive Dex or "usual care", with the target of light sedation (RASS score of +1 to -2), within 12 hours of mechanical ventilation.
- Usual care included Propofol, midazolam, and other sedatives and specifically excluded Dex, though "rescue" Dex could be used for uncontrolled agitation.
- Use of propofol and benzodiazepines was permitted in the Dex group if the max dose of Dex (1.5 mcg/kg/hr) failed to provide sufficient sedation. In these cases, the propofol dose was minimized and benzos were discouraged.
- Patients with traumatic and non-traumatic brain injury, those under 18 years old, and those on the ventilator more than 12 hours in the ICU were excluded.
- The primary outcome was all-cause mortality at 90 days after randomization.
- Secondary outcomes were 180-day mortality, 180-day cognitive function (measured by Short IQCODE questionnaire), discharge to nursing home or rehabilitation, and patient-reported health-related quality of life (measured by EQ-5D-3L questionnaire).
- The study was powered for 4000 patients with 90% power to detect an absolute difference of 4.5% in the primary outcome at a two-sided significance level of 0.05.

Findings
- Primary outcome data was obtained for 1948 Dex and 1956 usual care patients
- Approximately 28% of patients had surgery, and just under 5% were trauma patients
- Top four admission diagnoses were respiratory (~40%), sepsis, GI, and cardiovascular disorders (followed by trauma)

- All-cause 90-day mortality: 29.1% in both groups (p=0.98). No change after adjustment for baseline covariates
- No difference in mortality between pre-specified subgroups with or without sepsis (risk favoring Dex group by 1.1%), nor in the measures of cognitive function or health-related quality of life
- Median number of days free from coma or delirium (24 vs. 23), and the ventilator (23 vs. 22) both 1 day higher in the Dex group compared with usual care patients, respectively. However, no statistical tests of significance were done for these measures.
- Percentage of RASS scores in the target range in the first two days was higher in the Dex group (56.6%) vs. usual care (51.8%)
- In the Dex group, additional sedation was necessary using propofol (64.7%), midazolam (2.9%), or both (6.9%)
- Usual care group received propofol (60.1%), midazolam (11.9%), or both (20%) as their primary sedation
- Fentanyl given to 78.5% and 80.7% of those in the Dex and usual care groups, respectively.
- The Dex group had more adverse and serious adverse events, the majority of which were bradycardia and hypotension, as well as more asystole events (14 Dex patients, 0.7%, vs. 2 usual care patients, 0.1%; p=0.003).
- The only tertiary outcome with an odds ratio that did not cross 1 was the Dex group having higher odds of re-intubation (14.6% vs. 11.8%, OR 1.27 [1.06-1.53]).

Commentary

This study adds considerably to the literature on sedative infusions for mechanically ventilated patients. Similar to previous studies[1-3] it shows no survival benefit to dexmedetomidine compared to other commonly used agents, comparable sedative efficacy, and a marginal advantage with respect to ventilator days and delirium. Since the last two outcomes were not subjected to analysis for statistical significance, firm conclusions cannot be drawn about them. Also as in prior studies, complications of bradycardia and hypotension are more frequent with Dex, and the significantly higher rate of asystolic cardiac arrest in this study is alarming. The strengths of this study are the large number of patients, allowing its power to detect differences in mortality, which was a shortcoming of prior studies, and its measurement of longer term patient-centered secondary outcomes. Limitations are the lack of standardization for sedation and ventilator weaning among sites, its non-blinded methodology, lack of daily interruption of sedation, inclusion of patients who required deep sedation (as opposed to their target of light sedation), and lack of cost comparisons.

Implications for practice

Despite the size of this study and its addition to previous literature, the purported advantages of Dex as a primary sedative agent have still failed to elevate it to the level of “preferred agent” over other non-benzodiazepine based strategies, and certainly not to a standard of care. Its efficacy in brain injury patients (who are prone to agitation and delirium, and who would benefit from the ability to interact while receiving sedation) remains undetermined. The common theme of adverse cardiac events with Dex should prompt cautious and selective use in the ICU. Given that most patients receiving Dex needed additional sedatives, it seems its greatest benefit in this reviewer’s opinion is when used for short term sedation in patients expected to extubate within one or two days. Overall, one may consider dexmedetomidine as a reasonable option that is comparable to propofol- and fentanyl-based strategies.

References

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