Dexmedetomidine vs. Clonidine vs. Propofol for Sedation?

Key Article

- *Walsh TS, Parker MSc, Aitken LM, et al. Dexmedetomidine- or clonidine-based sedation compared with propofol in critically ill patients. The A2B randomized clinical trial. JAMA. 2025; Published online May 19, 2025.*

Background

- Critically ill patients receiving mechanical ventilation require sedation.
- At present, propofol is the most widely used sedative medication for ventilated patients.
- Recent trials have suggested that dexmedetomidine (alpha-2-adrenergic receptor agonist) may reduce delirium and duration of MV.
- Clonidine is also an alpha-2-adrenergic receptor agonist and is often used as an adjunct sedative in some countries.
- To date, there is no high-quality research that has evaluated dexmedetomidine or clonidine-based sedation to propofol in critically ill ventilated patients.

Objective

- To compare the effectiveness and safety of dexmedetomidine- and clonidine-based sedation vs. propofol-based sedation as the primary sedation for mechanically ventilated critically ill patients.

Methods

- Pragmatic, multicenter, open-label, randomized trial
- 41 ICUs in the UK
- Patients - Included
    - 18 years of age or older
    - Receiving mechanical ventilation in the ICU
    - Were sedated with propofol after intubation
    - Were within 48 hours of initiation of MV
    - Were expected to require a further 24 hrs or more of MV
- Patients – Excluded
    - Acute brain injury
    - Neuromuscular paralysis
    - Bradycardia (HR < 50 bpm for more than 60 minutes)
    - Expected survival < 24 hrs
- Intervention
    - Patients randomized in a 1:1:1 ratio
        - Dexmedetomidine
            - Initial dose 0.7 mcg/kg/hr
            - Max dose 1.4 mcg/kg/hr
        - Clonidine

        - Initial dose 1.0 mcg/kg/hr
        - Max dose 2.0 mcg/kg/hr
    - Propofol (Usual Care)
        - No specific dose guidance given
  - The open-label study drug was initiated within 2 hrs of randomization
  - Medical staff determined whether deep sedation (RASS -4 or -5) was indicated. If deep sedation was not indicated or requested, a RASS of -2 to 1 was targeted.
  - RASS measured every 4 hours, CAM-ICU measured every 12 hrs
  - Choice of an opioid for analgesia was determined by the clinical team.
  - Other sedatives (benzos) were discouraged.
  - **Propofol was permitted if the max dose of either dexmedetomidine or clonidine was reached or because of dose-limiting side effects.
  - MV weaning, sedation discontinuation, and assessing readiness for extubation guidance was provided but not protocolized.
- Primary outcome
  - Time from randomization to successful extubation
- Secondary outcomes
  - 180-day all-cause mortality
  - ICU LOS
  - Time to first RASS of -2 or greater
  - Time to first day without agitation, deep sedation, or pain behavior
  - Rates of delirium or coma
- Safety outcomes
  - Severe bradycardia
  - Cardiac arrhythmia
  - Cardiac arrest

Results

- A total 1404 patients were included in the analysis
  - Mean age: 59 years
  - 64% male
  - Mean APACHE II score: 20.3
  - Median time from initiation of MV to randomization: 21 hrs
- Allocation
  - Dexmedetomidine: 457 patients
  - Clonidine: 476 patients
  - Propofol: 471 patients
  - Baseline characteristics well balanced
- Primary Outcome
  - Dexmedetomidine vs. propofol: HR 1.09 (not statistically significant)
  - Clonidine vs. propofol: HR 1.05 (not statistically significant)
  - No significant difference in the number of patients receiving MV 7 days after randomization
- Secondary Outcomes
  - 180-day all-cause mortality
    - Dexmedetomidine vs. propofol: HR 0,98 (not statistically significant)
    - Clonidine vs. propofol: HR 1.04 (not statistically significant)

    - ICU LOS
        - No difference in time to ICU discharge among survivors
    - Time to first RASS -2 or greater
        - Median number of 12-hr nursing shifts to first achieve a RASS of -2 was 2 across all 3 groups
    - Time to first day without agitation, deep sedation, or pain behavior
        - Median of 3 days across all 3 groups
        - *Rates of agitation were higher over 7 days after randomization with both dexmedetomidine and clonidine
    - Rates of delirium or coma
        - No difference between the groups
- Safety Outcomes
    - Prevalence of bradycardia
        - Dexmedetomidine group: 33%
        - Clonidine group: 33%
        - Propofol group: 20%
    - Cardiac arrhythmia
        - Higher rates reported with dexmedetomidine vs. propofol (RR 1.27)

Limitations Identified by Authors

- Unblinded clinical trial
- Primary outcome measured by unblinded researchers
- Most patients in the dexmedetomidine and clonidine groups received propofol (approximately 77% of days), though at a lower dose than those in the propofol only group.
- Best practices for weaning, use of analgesia, and sedation targets were not protocolized.
- Findings cannot be extrapolated to patients with acute brain injury

Take Home Points

- A dexmedetomidine-based or clonidine-based sedation did not reduce the time to successful extubation in critically ill patients receiving mechanical ventilation when compared to propofol.
- No evidence of improved sedation quality or less delirium
- Higher rates of agitation and severe bradycardia in both the dexmedetomidine and clonidine groups