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Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation: Two Randomized Controlled Trials

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Background

- Dexmedetomidine may enhance patient safety and comfort in long-term sedation.
- It reduced the incidence of coma and delirium when compared with lorazepam, reduced duration of mechanical ventilation when compared with propofol or midazolam.
- A multi-centre trial found earlier extubation and reduced delirium with dexmedetomidine compared with midazolam.
- However, a recent meta-analysis presented inconclusive results for the effect of dexmedetomidine on duration of mechanical ventilation and ICU stay.

Aims

- 2 large, parallel, randomized controlled multicentre trials to compare dexmedetomidine with either midazolam or propofol.
- The study designs were identical except for the usual-care control drug.
- Assessed whether dexmedetomidine is noninferior to midazolam or propofol in maintaining mild to moderate sedation
- Reduced mechanical ventilation and ICU stay and patients' ability to communicate during sedation.

Methods

- European, multi-centre, randomized, double-blind studies conducted in 2007 - 2010
- midazolam vs. dexmedetomidine (MIDEX trial; 44 centers in 9 European countries)
- propofol vs. dexmedetomidine (PRODEX trial; 31 centers in 6 European countries and 2 in Russia)
- The main inclusion criteria were age 18 years or older, invasive mechanical ventilation, clinical need for light to moderate sedation

Randomization and Masking

- Eligible study participants were randomized 1:1 by a central interactive voice-response system.
- Remain on standard treatment or switch to dex.
- All patients and study personnel were masked to treatment allocation.
- ‘Treatments were administered in a double-dummy design, with 0.9% sodium chloride as dummy for all treatments.’ (?)
- ‘Propofol and propofol dummy were prepared, connected, and removed by independent personnel and infused with nontransparent black syringes, infusion tubings, and connectors.’

Methods - Sedation

- Target RASS score was determined before starting study treatment and at daily sedation stops.
- Assessment of RASS score was performed every 2 hours and prior to any dose of rescue therapy.
- Study treatments were infused without loading dose at a dose matching the prerandomization dose of midazolam (MIDEX trial) or propofol (PRODEX trial) for 1 hour.
- Thereafter, study drugs were titrated by the patient's nurse stepwise to maintain the target RASS score
- Rescue medication boli could be given if needed to achieve target RASS score

Outcomes

- primary end point = proportion of time in target sedation range (RASS score, 0 to -3) without use of rescue therapy
- duration of mechanical ventilation from randomization.
- Secondary efficacy outcomes were length of ICU stay from randomization until medically fit for discharge
- and nurses' assessment of arousal, ability to cooperate with care, and ability to communicate pain using visual analogue scales (VAS).

Stats

- The planned enrolment was 500 participants in each trial.
- Based on a pilot study, they assumed an overall 64% of time in target range of sedation without using rescue medication.
- A sample size of 450 in each trial gives 90% power to reject a 15% inferiority of dexmedetomidine to standard sedation

Results

- 249 and 251 patients in the dexmedetomidine and midazolam groups (MIDEX trial) and 251 and 247 patients in the dexmedetomidine and propofol groups (PRODEX trial)
- time at target sedation without rescue medication: midazolam, 56.6%, vs dexmedetomidine, 60.7%; propofol, 64.7%, vs dexmedetomidine, 64.6%
- Study drug discontinuation rates were similar in dexmedetomidine and standard care patients (approx. 25%)

Results

- The median duration of mechanical ventilation in MIDEX was 164 hours (IQR, 92-380 hours) for midazolam and 123 hours (IQR, 67-337 hours) for dexmedetomidine (P = 0.03).
- In PRODEX, it was 118 hours (IQR, 48- 327 hours) for propofol and 97 hours (IQR, 45-257 hours) for dexmedetomidine (P = 0.24)

Results

- The median length of stay in the ICU from randomization until the patient was medically fit for discharge was not significantly different in the 2 studies
- Patients receiving dexmedetomidine were more arousable, more cooperative, and better able to communicate their pain than patients receiving either midazolam or propofol ($P<0.001$ for each component separately and for total VAS score)

CV complications

- In the MIDEX trial, hypotension was recorded in 29 of 250 midazolam patients (11.6%) vs 51 of 247 dexmedetomidine patients (20.6%) (P =.007).
- Bradycardia was reported in 13 of 250 midazolam patients (5.2%) and in 35 of 247 dexmedetomidine patients (14.2%) (P <.001)
- First-degree atrioventricular block in MIDEX was observed in 3 patients in each group and, in PRODEX, in 2 propofol patients (0.8%) and 9 dexmedetomidine patients (3.7%) (P = 0.04).

Neurological complications

- Critical illness polyneuropathy was less common in patients receiving dexmedetomidine than in those receiving propofol (2 patients vs 11 patients; P = .02).
- In the MIDEX trial, rates of neuro-cognitive adverse events through 48 hours of follow-up (agitation, anxiety, delirium,) were not different between midazolam and dexmedetomidine patients.
- In PRODEX, neurocognitive adverse events were reported in 71 of 247 propofol patients (29%) and in 45 of 251 dexmedetomidine patients (18%) (P = .008)

Comments

- Confirmed Dexmedetomidine's non-inferiority compared with these standard sedation strategies in mild to moderate sedation
- Dexmedetomidine appeared to shorten mechanical ventilation compared with midazolam but not compared with propofol
- Dexmedetomidine enhanced patients' ability to communicate pain to the nursing staff.
- With the current maximum dose, lack of efficacy can be expected in approximately 1 in every 8 to 10 patients.

Limitations

- since the study drug was limited to 14 days, but mechanical ventilation was considered up to 45 days, standard care given after dexmedetomidine may have reduced any benefit from dexmedetomidine.
- The standard sedation preceding randomization may have masked benefits of dexmedetomidine during shorter exposure.
- They assessed sedation from the caregiver's perspective. Future studies should include the patient's perspective of quality of sedation as well

Summary

- Shorter MV compared with midazolam
- ICU LOS - no difference
- Better cooperation/comm. of pain
- Significant CV complications with Dex
- More polyneuropathy in propofol group
- More neuro-cognitive adverse events in propofol group (but not midazolam)
- Some confounding factors in design