

Dexmedetomidine the Delirium Deterrent

A(Lpha) grade sedation for the invasively ventilated?

Nepean WTET summary 12/5/20

Background and Rationale

- Sedation practice (from primary agents, to depth and duration) in intensive care varies widely across the globe. In general there has been a move away from midazolam and towards propofol in the adult population, but conversely away from propofol in the paediatric population (due to concerns of propofol infusion syndrome). The use of newer agents (e.g. dexmedetomidine) and shorter acting opiates (e.g. remifentanyl) has steadily moved over from anaesthetic practice and into the ICU
- Traditional first line sedative agents (propofol and midazolam) act mainly through GABA. These are often used in conjunction with an opioid for analgesic (+/-antitussive) for tube tolerance purposes
- Dexmedetomidine is a titratable alpha2 agonist administered by continuous intravenous infusion. It both facilitates conscious sedation and provides analgesia
- Experimental evidence suggests a potential protective effect (of dexmedetomidine) against neuronal, myocardial and renal injury. Similarly it has been shown to reduce inflammation in sepsis (with reduced delirium and mortality) and post bypass
- There is some evidence that dexmedetomidine may potentiate hypoxic pulmonary vasoconstriction (HPV) so assist in protection against shunt (one lung ventilation studies)

Advantages and Disadvantages

- Advantages;
 - Both analgesic (synergistic) and sedative properties
 - Conscious sedation facilitates improved communication (and participation in physio etc...)
 - May have anti-inflammatory properties (large portion of ICU patients present with an inflammatory state) and may preserve HPV (critically ill are high risk of atelectasis and shunt)
 - Titratable infusion
 - Can be used safely in non-ventilated patients (monitored)
- Disadvantages;
 - Cost (now less of an issue) – a more expensive reiteration of an old drug (clonidine)
 - Off-label use (recommended for initial sedation only in critically ill ventilated patients only up to max 24h, not for sedation in non-ventilated patients outside perioperative setting) at above recommended concentrations (recommend up to 0.7mcg/kg/h in ICU setting, up to 1.0mcg/kg/h for procedural sedation)
 - Bradycardia (relatively contraindicated in high grade AV block) to include asystole, hypotension. Tachyphylaxis and tolerance (increasing doses → increased adverse events). Associated with acute colonic pseudo-obstruction
 - Cannot bolus for rapid deepening of sedation, delayed clinical response to changes in dosing

Evidence

- MIDEX-PRODEX 2012 JAMA
 - Non-inferiority of midazolam versus dexmedetomidine (one RCT) and propofol versus dexmedetomidine (second RCT) -double blinded (concealed infusions) European study
 - Approx. 250 in each treatment arm (midaz/ppf/dexmed); dexmedetomidine non-inferior
 - Reduced duration of mechanical ventilation with dexmedetomidine (statistically significant when compared to midaz), less neuropathy compared to propofol, better communication
- SPICE (Au/Nz) Am J Resp and Crit Care Med 2012
 - Prospective longitudinal cohort study (25 ICUs) ventilated >24h, RASS 4hrly, 180d mortality
 - Deep sedation within 4h of invasive ventilation *independent* negative predictor of time to extubation, time to delirium (CAM-ICU) and 180d mortality
 - Cumulative midazolam and fentanyl dose within 48h predicted time to extubation *independent* of sedation depth (propofol and morphine did not)
 - Conclusion; *Early* sedation depth impacts outcomes therefore important to investigate *early* sedation practices (rather than late) – early interventions with delayed consent appropriate
- SPICE (Malaysia) 2013 Intensive Care Med
 - Same study design, 11 ICUs, reiterated similar findings; early deep sedation independently associated with delayed extubation and higher hospital and 180d mortality
- DahLIA trial JAMA 2016
 - Double blinded RCT of dexmedetomidine vs placebo for mechanically ventilated patients where extubation is precluded due to presence of marked agitated delirium. 15 ICUs, n=74
 - 144.8h versus 127.5h ventilator free hours at 7 days (statistically significant, P=0.01)
- Skrobik et al 2018 J Resp and Critical Care Med
 - Prospective phase 2 RCT: 2 center (Boston/Quebec), ICU patients expected to be in ICU >48h receiving continuous or intermittent sedatives, who do not already have delirium; n=100
 - Nocturnal dexmedetomidine vs 5% dextrose (blinded) 1:1 randomisation. All pre-existing sedatives halved, study drug titrated to RASS -1 (using dose range 0.1-0.7mcg/kg/h IBW) starting 21:30 every night and using last effect dose
 - Significant reduction in number of patients delirium-free during critical illness 80% vs 54% using ICDSC (Intensive Care Delirium Checklist Screening Checklist) =/ >4
- SPICE3 NEJM 2019
 - 8 countries, 74 ICUs, n=4000. Stratified (by site) block randomisation 1:1 of sedation practice. Both groups targeting light sedation (RASS -2 to +1) monitored 4hrly, delirium (CAM-ICU) daily
 - Dexmedetomidine (starting 1mcg/kg/h, titrated up to max 1.5mcg/kg/h, can add low dose propofol if required for RASS, midazolam discouraged unless seizures etc) vs usual care (excluding dexmedetomidine use); open-label
 - Incl.: adults without primary brain pathology, deep sedation not indicated, intubated <12h
 - Primary outcome 90d mortality not improved with dexmedetomidine however better targeted sedation (achieving RASS) and 1 day more free from mechanical ventilation. More bradycardia, hypotension and asystole in dexmedetomidine group.
 - Overall, no benefit in a large heterogenous group; ?subgroups may benefit? Over the median age (63.7y) there was significantly lower mortality → enter SPICE 4 asking ?benefit in elderly?

Summary (my practice)

- Currently I do not use dexmedetomidine as a first line sedative agent at the time of intubation. I may switch to or add it in over the course of a patients admission in particular in patients where pain is difficult to manage (analgesic adjunct), high levels of sedation is required or where substance misuse and/or agitated delirium precludes a safe wake-up and extubation. In the latter group I prefer a trial of clonidine to assess response prior to committing to an infusion (slower onset time). Similarly I am mindful of avoiding prolonged infusions with regards to evolving tachyphylaxis
- I avoid dexmedetomidine in those with high grade AV block (second degree heart block or higher), symptomatic or severe bradycardia and those patients particularly at risk of Ogilvie's syndrome
- I await the SPICE 4 trial to guide its use as a first line agent in the elderly.