

# NMBA and ARDS

*Nepean WTET summary 24/3/20*

## Background and Rationale

- Management of ARDS is first and foremost targeted towards treatment of the underlying cause/driver and secondly prevention of further injury -ventilator induced lung injury (VILI) with a lung protective ventilation (LPV) strategy
- Neuromuscular blocking agents (NMBA) aim to completely negate ventilatory dyssynchrony which can contribute in particular to high transpulmonary pressures and barotrauma.
- In an attempt to prevent VILI it makes sense to instigate this management strategy earlier rather than later when it might be too late
- Atracurium was the main NMBA in critical care use when an association was made with prolonged muscle weakness. Steroid use had shown to have similar effects. Therefore concerns exist with steroidal NMBA (pancuronium, vecuronium or rocuronium) in particular, that they may carry the highest risk of myopathy of all the NMBA; as such (without strong reasoning) cisatracurium became the primary agent of choice in many institutions
- The population who have most to gain from paralysis as a management strategy are those with higher disease severity, where benefits may outweigh potential harms

## Advantages and Disadvantages

- Advantages;
  - More control over tidal volumes and transpulmonary pressures, with fewer pneumothoraces in this high-risk population
  - Required for proning (at least initial treatments) which demonstrated high mortality benefit (see earlier WTET) in this population
  - Cheap and easy to do; monitoring with train-of-four (TOF)
- Disadvantages;
  - Paralysis shown to be an independent risk factor for critical illness weakness (some degree of association likely, but plausible element of causation also)
  - Need for deep sedation (awareness) with associated drug side effects; haemodynamic instability, blunting of hypoxic pulmonary vasoconstriction
  - More haemodynamic instability independently associated with NMBA use (vasodilatory?) when compared to deep sedation alone

## Evidence

- Early small studies showed improvement in oxygenation and a trend towards a mortality benefit; however underpowered for mortality (which is a; patient-orientated endpoint that matters; POEM) hence...
- ACURASYS 2010
  - MC double-blinded trial, n=340, European
  - American-European consensus ARDS definition used
  - Randomised ARDS P/F<150, early (<48h) to 48h cisatracurium vs placebo (median time to randomization was 16h); deep sedation in both arms
  - Primary outcome; mortality <90d or before hospital discharge (adjusted for P/F, plateau pressure and APACHE2); 31.6% in cisatracurium vs 40.7% in placebo
  - VT 6-8ml/kg (PBW) and a low PEEP strategy (median 9.2); higher pneumothorax in placebo group 11.7% vs 4%, no difference in weakness
  - ?Underpowered; as showed lower mortality than previous studies
  - Post hoc; benefit really only to those with P/F<120

- ROSE 2019
  - MC unblinded trial, n=1006 (stopped early for futility), American
  - Berlin ARDS definition used
  - Randomised ARDS P/F<150 PEEP =/>8 to deep sedation and 48h cisatracurium versus 'usual care' (no routine NMBA and lighter sedation)
  - Primary end point death <90d in hospital (same); 42.5% vs 42.8%
  - LPV strategy in both arms, higher PEEP (median 12.5), lower VT (median 6.3ml/kg PBW) compared to ACURASYS
  - No (statistically significant) difference in pneumothorax but increased CVS instability in NMBA group
  - NB 25% of control arm received NMB; in 15% of treatment arm NMB stopped early due to clinical improvement
  - Only 20.7% of eligible patients included -commonest reasons for exclusion include;
    - P/F>200 at time of randomisation (nicely demonstrates limitations of P/F as a marker of severity)
    - Already receiving NMBA → ?exclusion of those patients who would benefit, because of clinician selection of appropriate patients

### Summary (my practice)

- NMBA assist in delivering LPV as a strategy in those whom it is difficult
- Some patients with severe ARDS may have severe hypoxia without significant problems with compliance or dyssynchrony and so probably have little to benefit outside intentions of increasing the safety profile of protocolised proning or recruitment maneuvers
- NMBA is not a treatment for ARDS in its own right and therefore patient selection on a case-by-case is needed; it should not be considered as a standard approach to all-comers with moderate-severe ARDS
- I therefore use NMBA in those patients with ARDS who have poor lung compliance threatening LPV strategies or those in whom deep sedation alone is inadequate (or unsafe) to manage ventilator dyssynchrony
- I use cisatracurium, early (<48h of moderate-severe ARDS) and for short durations where possible; but again with an individualised approach of benefit versus harm (no studies looking at late or prolonged paralysis) with regular review of ongoing need