

Inspired (by) Nitric in ARDS?

Nepean WTET summary 7/4/20

Rationale and Background

- Main mechanism driving hypoxia in ARDS is shunt
 - This may be further exacerbated by pharmacological blunting of our physiological protective mechanisms (hypoxic pulmonary vasoconstriction) by use of deep sedation in these patients
 - Hypoxia due to significant shunt responds very poorly to increases in FiO_2 -with a potential paradoxical fall in PaO_2
 - Pulmonary vasodilators such as iNO improve V/Q matching and thereby reduce shunt and improve oxygenation irrespective of FiO_2
 - If hypoxia is considered to be the main driver behind MOF and death in ARDS then improving oxygenation should lead to improved morbidity and mortality. On the other-hand effects of iNO are short-lived and do not treat underlying pathology, -so on its own as a treatment, other than buying time (short-lived: tachyphylaxis) it may not improve outcomes
- Other strategies for improving oxygenation in ARDS include increasing mean airway pressure; whilst this may recruit alveoli and improve gas exchange it potentially may increase RV afterload (which we know already to be acutely elevated as part of ARDS pathophysiology)
 - This is individual, as the effect of increased intrathoracic pressure on RV afterload may be offset/balanced by the beneficial effect on the RV of improved oxygenation / CO_2 clearance
 - iNO shown to be effective in treatment of pulmonary hypertension and reducing RV afterload (especially in neonates)

Advantages and Disadvantages

- Advantages;
 - Good physiological rationale; improves oxygenation and RV afterload -both of which are a problem in ARDS and which may contribute to M&M and reduced ventilator-free days
 - Cheap, readily accessible in most ICUs, minimal additional training required to use
- Disadvantages;
 - Practical: Requires scavenging / adequate air changes, monitoring for potential toxic NO_2 levels, dedicated inserts increase dead space of circuit
 - Physiological: May cause systemic hypotension, associated AKI, pulmonary oedema (if LV dysfunction), platelet inhibition may increase bleeding, methaemoglobinaemia, if complications cannot rapidly wean/discontinue (rebound PHtn and hypoxia), increase ICP
 - Other: not all patients are responsive, dose-response unclear, tachyphylaxis occurs (short-term treatment)

Evidence

- A number of small RCTs exist – randomising patients with varying severity of ARDS into iNO versus placebo / no treatment. A variety of dose ranges and protocols were used to include identification of responders and use of differing dosing regimens (low dose to high dose tried)
- Cochrane review 2016 (adults and children with ARDS)
 - 14 trials (1275 participants)
 - No effect on 28d mortality or ventilator free days
 - Improved P/F (and/or oxygenation index) at 24h
 - Increase in renal failure in iNO group
 - Cannot recommend as a treatment in this group

Summary (my practice)

- I do not use iNO routinely in my management of severe ARDS
- I do use it for short periods (<48h) in those with severe refractory hypoxaemia ($SaO_2/SpO_2 < 85\%$) refractory to conventional ventilation strategies, as a bridge to another intervention with a better evidence-base of benefit e.g. proning, ECMO
- I individually weigh-up potential risks of benefit-harm, start low (5ppm) and slowly increase up to a maximum of 20ppm – if unresponsive at 20ppm I do not expect to see a benefit increasing beyond this and am likely to experience marked worsening in systemic hypotension etc., I am vigilant for other anticipated complications
- I ensure adequate monitoring and scavenging systems are in place and staff are familiar with its use
- If non-responsive or marked complications, I wean and discontinue this therapy early