The ROSE Trial

The Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network of the National Heart, Lung, and Blood Institute (NHLBI) conducted the Re-evaluation of Systemic Early Neuromuscular Blockade (ROSE) trial — a multicentre, unblinded, randomized trial of patients with moderate-to-severe ARDS

What's Known -

Neuromuscular blockade reduces patient–ventilator dyssynchrony, the work of breathing, and the accumulation of alveolar fluid; patients with ARDS could benefit from these outcomes. However, prolonged administration of neuromuscular blocking agents is associated with subsequent neuromuscular weakness.
ACURSYS trial in 2010 suggested possible mortality benefit with the use of early NMB.

Question-
to determine the efficacy and safety of early neuromuscular blockade with concomitant heavy sedation as compared with a strategy of usual care with lighter sedation targets.

Hypothesis -
The use of early neuromuscular blockade would result in lower all-cause in-hospital mortality at 90 days than usual care.

Methods-
A multicentre, unblinded, randomized controlled trial

Trial Design -
Permutational block design stratified by site, assigning patients in 1:1 ratio
For 90% power with two-sided alpha 0.05, 1408 patients required (based on control group mortality 35% and intervention group 27%)

48 ICUs in the United States
Jan 2016-April 2018 - 1006 patients

- **Inclusion Criteria**:
  - P/F ratio <150 mmHg (22 kPa)
  - PEEP>8 cm H2O

    - Bilateral opacities on CXR/CT that could not be explained by effusions, pulmonary collapse, or nodules
    - Respiratory failure that could not be explained by cardiac failure or fluid overload
    - Onset of illness within one week of known clinical insult or new/worsening respiratory symptoms
- **Exclusion Criteria**:
    - Refusal of consent
    - Neuromuscular blockade at prior to enrolment
    - Pregnant
    - ECMO at time of assessment
    - Chronic respiratory failure (defined as pCO2 >8 kPa in outpatients)
    - Home ventilation
    - BMI >100
    - Severe chronic liver disease
    - Bone marrow transplant within last year
    - Expected mandatory ventilation duration <48 hours
    - Decision to withhold life-sustaining therapy
    - Moribund and not expected to survive 24 hours
    - Diffuse alveolar haemorrhage from vasculitis
    - >70% BSA Burns
    - Unwillingness/unable to stick to ARDSnet 6mL/kg protocol
    - Hypersensitivity to cisatracurium
    - Neuromuscular conditions that may potentiate NMB/inhibit spontaneous ventilation
    - Neurological conditions undergoing treatment for intracranial hypertension
    - Enrolment in an interventional ARDS trial with direct impact on neuromuscular blockade/PEEP
    - P/F ratio >200 mmHg (32 kPa) after meeting inclusion criteria and before randomisation
    - Ventilation >5 days
    - On lung transplant list

4848 patients screened; 1006 patients included in primary analysis.

Intervention Group - n = 501
Deep sedation within four hours of randomisation
15 mg bolus of cisatracurium, followed by 37.5 mg/h infusion

Control Group - n= 505
to receive usual care without routine neuromuscular blockade and with lighter sedation targets i.e Light sedation, RAAS to -1 or equivalent on Richter scale

Both groups -
Low tidal volume ventilation within two hours of randomisation, with high PEEP for up to five days

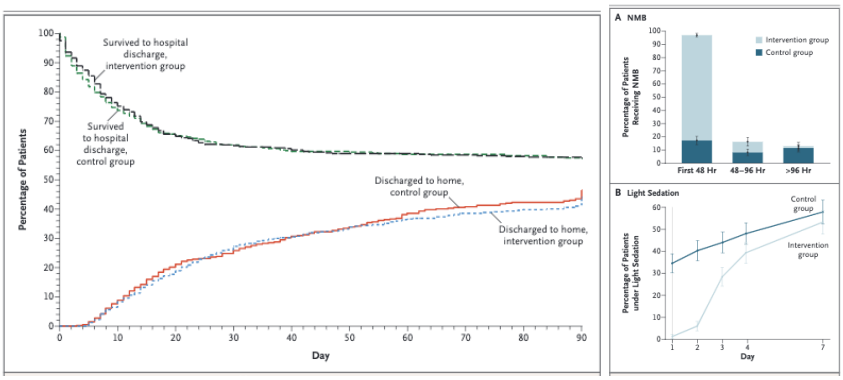
Comparison with ACURSYS -
Similarities included the use of the same neuromuscular blocking agent (cisatracurium) with the same dosing regimen and duration of treatment.
A key difference was use of lighter sedation targets in the control group to be consistent with current practice recommendations.
the use of a strategy involving a high PEEP, and
the use of a conservative fluid strategy.

Results -

Primary outcome: 90- Day mortality
42.5% (intervention) vs 42.8% (control)
Secondary outcome:
No significant difference seen in secondary outcomes
These were -

- ICU acquired weakness
- 28-day mortality
- Ventilator-free days at day 28
- Organ failure-free days till day 28
- ICU-free days at day 28
- Hospital-free days at day 28
- Long term assessments of quality of life
- Use of rescue procedures e.g ECMO
- Awareness/recall

*** Incidence of CVS adverse events higher in Intervention group
The use of adjunctive therapies appeared to be similar in the two groups during the 48-hour intervention period



Strengths -

- Randomised
- Intention to treat analysis
- Large sample size
- Sick patients- P/F -100, FiO2-80%, SOFA -8, APACHE III 100, 70%patients with Shock
- good adherence to the protocol with respect to PEEP and Fio2 recommendations, and adherence to recommended ventilation guidelines ranged from 80.1 to 87.5% with respect to low tidal volume ventilation (≤6.5 ml per kilogram of predicted body weight) and 85.6 to 90.8% with respect to low plateau pressures (≤30 cm of water). The median daily fluid balance was 327 ml (interquartile range, −951 to 1456) on day 2 and −242 ml (interquartile range, −1432 to 728) on day 3, and there were no differences between trial groups.
- 1-year follow up
- Patient related outcomes 3,6,12 months.

Limitations -

- Unblinded
- ?? External validity - as all patients are recruited from US.
- Large loss of patients at screening- due to
    - improvement between screening and inclusion (658) and
    - patients having already received neuromuscular blockade (655)
- The 655 patients who received neuromuscular blockade may have biased the results in favour of the control group
- Depth of neuromuscular blockade not measured
- Stopped for futility - which makes ROSE an underpowered study
- Less use of Proning

Conclusions-

Well conducted RCT with significant contribution to our understanding of ARDS.

ARDS still remain the major healthcare problem- 42% mortality

N-M blockade does not reduce mortality at 90 days in severe ARDS, however incidence of N-M weakness is not high

N-M blockade may be still beneficial for select cohort of patients

Lighter sedation is okay - Time to challenge the dogma of blanket use of Deeper sedation for all ARDS patients

Less adoption of Prone Ventilation (15%)