Are Neuromuscular Blockers Helpful in ARDS?

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Objectives

- Indications for using neuromuscular blockers to improve patient-ventilator interaction and perhaps outcome in ARDS
- Potential complications of sedation and neuromuscular blockade
- Guidelines and considerations for use of neuromuscular blockade
What is the rationale for early paralysis in ARDS?
Mechanisms by Which NMBAs Might Lead to Improved Survival in Patients with ARDS

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NMBAs improve oxygenation in ARDS

- 56 ARDS pts randomized to ± cisatracurium infusion for 48 h

- Compared to controls:
  - PaO2/FiO2 improved
  - PEEP decreased
  - Peak & plateau airway pressure decreased
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NMBAs ↓ inflammatory response in ARDS

- 36 ARDS pts randomized to + cisatracurium infusion for 48 h.
- PaO$_2$/FiO$_2$ improved in NMBA group
- BAL IL-8, IL-6 & IL-1$\beta$ & serum IL-1$\beta$ and IL6 lower in NMBA group at 48 h.
- BAL cell count and TNF$_{\alpha}$ no different
- Duration of MV, MV free days, and mortality not different
- Effect of the drug or pattern of ventilation?
Neuromuscular Blockers in Early ARDS

- 340 ARDS pts (PaO$_2$/FiO$_2$ < 150 mmHg) in 20 French ICU’s
- Randomized to ± cisatracurium infusion: 15 mg bolus, then 37.5 ml/hr for 48 h
- Reduced adjusted mortality at 28 days from 33.3 to 23.7%
Neuromuscular Blockers in Early ARDS

Beneficial effect limited to patients with $\text{PaO}_2/\text{FiO}_2 < 120$
Neuromuscular Blockers in Early ARDS

Probability of Breathing Without Assistance
Neuromuscular Blockers in Early ARDS

Patients with Pneumothorax
What are the risks?
Disadvantages of NMBAs

- Effect on PaO$_2$ variable
- Increased atelectasis
- Cephalad displacement of diaphragm
- Airway closure
Problems with Muscle Relaxants

- Danger of disconnects
- Elimination of cough
- Hinder neurologic & psychologic evaluation
- Prolonged blockade
- Myopathy/Neuropathy
Overdose of Muscle Relaxants

- An awake but paralyzed patient
  - “A mind entombed in a corpse”
- A paralyzed patient in pain
- Possible nerve & muscle damage
- Difficult and prolonged reversal
What is the impact on muscle function?
Prolonged Paralysis following Neuromuscular Blockade

Prolonged Paralysis following Neuromuscular Blockade

Neuromuscular Weakness

Prospective controlled trial
Examined 73 septic patients with multi-organ failure in the ICU
63% developed critical illness polyneuropathy (CIP) after 10 days of mechanical ventilation
  - As diagnosed by sensory and motor nerve conduction studies
Neuromuscular Weakness

• Of the 50 patients that developed CIP...
  – 9 received NMB (6 vecuronium, 3 atracurium)
  – Only 1 patient in the non-CIP group received NMB

• Multivariant analysis found independent RFs for the development of CIP

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
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<tbody>
<tr>
<td>Hyperosmolality</td>
<td>4.8</td>
<td>1.05–24.38</td>
<td>0.046</td>
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<tr>
<td>Parenteral nutrition</td>
<td>5.11</td>
<td>1.14–22.88</td>
<td>0.02</td>
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<td>Use of NMBAs</td>
<td>16.32</td>
<td>1.34–199</td>
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<td>Neurologic failure</td>
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<td>3.68–156.7</td>
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<tr>
<td>Renal replacement therapy</td>
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<td>0.05–0.15</td>
<td>0.001</td>
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</table>

a GCS below 10
Neuromuscular Weakness

- Other trials have NOT been able to demonstrate this association:
  - Papazian L, et al. NEJM 2010, 363:1107-16
Neuromuscular Weakness

- Risk factors implicated in the development of critical illness polyneuropathy and myopathy:
  - Severity of illness
  - Female gender
  - Duration of organ dysfunction and duration of ICU stay
  - Renal failure or RRT
  - Hyperosmolality
  - TPN
  - Vasopressor support
  - Central neurologic failure (GCS <10)
  - Hyperglycemia
  - Corticosteroids
  - Neuromuscular blockade

Monitoring and Titrating

- Depth of neuromuscular blockade should be assessed by train-of-four (TOF) monitor
- Drug should be titrated to achieve 1-2 twitches in TOF
Peripheral nerve stimulation vs. standard clinical dosing of NMBAs in critically ill patients


- Prospective randomized single-blind trial in 77 pts of PNS monitoring (T4 1:4) vs. clinical response to vecuronium
- PNS group
  - Used less drug/hr
    (0.028 vs 0.07 mg/kg/hr)
  - Less total drug
    (286 vs. 106 mg)
  - Recovered neuromuscular function (RR 1.89) & spont ventilation faster (RR 2.27)
# Available NMB Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Active Metabolite</th>
<th>Metabolism</th>
<th>Elimination</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>Pancuronium</td>
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<td>Liver</td>
<td>Renal excretion</td>
<td>Vagolytic</td>
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<td>Vecuronium</td>
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<td>Liver</td>
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<tr>
<td>Rocuronium</td>
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<tr>
<td>Atracurium</td>
<td>No</td>
<td>No</td>
<td>Hofmann elimination*</td>
<td>Histamine release</td>
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<td>Cisatracurium</td>
<td>No</td>
<td>No</td>
<td>Hofmann Elimination*</td>
<td>None</td>
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</table>

* Hofmann elimination = spontaneous degradation in the plasma, independent of organ function
Supportive Care

- Remember to...
  - Ensure adequate sedation and analgesia prior to neuromuscular blockade
  - Frequent turning and pressure point padding to avoid pressure ulcers
  - Elevate HOB to decrease aspiration and VAP
  - Suction based on secretions as patient will not have cough reflex
  - Very close supervision and avoidance of ventilator disconnections
  - Apply eye lubrication and/or cover eyelids to avoid corneal abrasions
Use of NMBA’s in ARDS

• Supportive evidence provided by 3 randomized studies – all from the same group
• No data to support use for other than severe ARDS
• Use of neuromuscular blockade should be rare
  – Should have little need beyond > 48 hr
• Avoid corticosteroids and steroidal NMBAs (e.g., vecuronium, pancuronium)
• Discontinue NMBAs As soon as practical