Neuromuscular Blockade in ARDS

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Disclosures

None
Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

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Possible Mechanisms

Lung mechanics
- Better synchrony
- More uniform recruitment
- Improved compliance
- Better gas exchange
- Better systemic oxygenation

Lung inflammation
- Better control of insp V, P
- Less volutrauma
- Better control of exp V, P
- Less atelectrauma
- Less lung inflammation
- Less systemic inflammation
Trade-offs

**Potential benefits**
- Synchrony
- Oxygenation
- Reduced VILI
- Survival

**Potential harms**
- Prolonged weakness
- Hemodynamics
- Cost
Paralysis and Prolonged Weakness

Overview
• case reports, case series, retrospective studies
• usually related to asthma, confounded by steroid use
• lacked objective, reliable measures
• lacked systematic screening

Findings
• risk of prolonged weakness was related to dose, duration, and coexistent renal or hepatic dysfunction
• role of a class effect controversial
  – Aminosteroids (pancuronium, vecuronium, rocuronium) vs benzylisoquinolines (cisatricurium)
Prospective, controlled study (N = 73)

All received electrophysiologic testing
- Sensory and motor nerve conduction
- Blinded assessments

14% received NMBA; 15% received steroids

50% developed critical illness polyneuropathy

18/73 survived; 8 had polyneuropathy (44%)

OR 16.3 (1.3 – 199), p 0.0008
- regardless of NMBA class
- steroids not associated with weakness (NS)
ICU physician survey 2002


• Agents (across indications)
  – pancuronium, rocuronium, vecuronium
  – ...cisatricurium

• Monitoring
  – 61% physical exam
  – 84% PNS

• Daily interruption
  – 64% discontinued paralysis on a daily basis

• Protocols
  – 22% used a local protocol for neuromuscular blockade
Actual Use of NMBA

- **ALVEOLI (P/F ≤ 300)**... 25% ever, median 2 days
- **EXPRESS (P/F ≤ 300)**... 63% ever, median 3 days
- **LOVS (P/F ≤ 250)**... 44% ever, median 2.5 days

- **OSCILLATE**
  - (P/F ≤ 200)... 32.8% at baseline

- Randomized trials of low tidal volume ventilation
  - Burns, PLoS 2011
  - Compared to patients receiving traditional ventilation, significantly more patients managed with low Vt received paralysis
  - RR 1.37; 95% CI 1.04-1.82; p=0.03
ACURASYS

Design... multicentre RCT

Patients... 340 patients with ARDS
- early (< 48h)
- severe (P/F < 150)
- PEEP ≥ 5 cm H₂O; Vt 6-8 ml/kg

Paralysis... cisatricurium infusion x 48 h

Control... placebo infusion x 48 h

Both groups... - deep sedation
- lung protective volume-AC
- 20 mg cisatricurium injection if Pplat > 32 cm H₂O
- no peripheral nerve stimulation

Analysis... adjusted RR hospital mortality at 90 days
(P/F, SAPS II, Pplat)
Mortality at 90 Days

Hazard Ratio 0.68 (0.48 – 0.98) p = 0.04
# Meta-analysis: ICU Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cisatracurium</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Gainnier 2004</td>
<td>13</td>
<td>28</td>
<td>27.2%</td>
</tr>
<tr>
<td>Forel 2006</td>
<td>5</td>
<td>18</td>
<td>8.0%</td>
</tr>
<tr>
<td>Papazian 2010</td>
<td>52</td>
<td>177</td>
<td>64.8%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>223</strong></td>
<td><strong>208</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

**Total events** 70 93

Heterogeneity: \( \tau^2 = 0.00; \chi^2 = 0.95, \text{df} = 2 (P = 0.62); I^2 = 0\%

Test for overall effect: \( Z = 2.88 (P = 0.004) \)

With permission, Dr. Waleed Alhazzani
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cisatracurium (N=177)</th>
<th>Placebo (N=162)</th>
<th>Relative Risk with Cisatracurium (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no. (% [95% CI])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 28 days</td>
<td>42 (23.7 [18.1–30.5])</td>
<td>54 (33.3 [26.5–40.9])</td>
<td>0.71 (0.51–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>In the ICU</td>
<td>52 (29.4 [23.2–36.5])</td>
<td>63 (38.9 [31.7–46.6])</td>
<td>0.76 (0.56–1.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>In the hospital</td>
<td>57 (32.2 [25.8–39.4])</td>
<td>67 (41.4 [34.1–49.1])</td>
<td>0.78 (0.59–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>No. of ventilator-free days†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From day 1 to day 28</td>
<td>10.6±9.7</td>
<td>8.5±9.4</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>From day 1 to day 90</td>
<td>53.1±35.8</td>
<td>44.6±37.5</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>No. of days without organ failure, from day 1 to day 28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cardiovascular failure</td>
<td>18.3±9.4</td>
<td>16.6±10.4</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>No coagulation abnormalities</td>
<td>22.6±8.9</td>
<td>20.5±9.9</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>No hepatic failure</td>
<td>21.3±9.6</td>
<td>19.1±10.6</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>No renal failure</td>
<td>20.5±10.1</td>
<td>18.1±11.6</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>None of the four</td>
<td>15.8±9.9</td>
<td>12.2±11.1</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>No. of days outside the ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From day 1 to day 28</td>
<td>6.9±8.2</td>
<td>5.7±7.8</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>From day 1 to day 90</td>
<td>47.7±33.5</td>
<td>39.5±35.6</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Hospital survivors admitted to other health care facilities from day 1 to day 90 — % (95% CI)</td>
<td>22.3 (15.8–30.5)</td>
<td>18.8 (12.2–27.8)</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Barotrauma — no. (% [95% CI])‡</td>
<td>9 (5.1 [2.7–9.4])</td>
<td>19 (11.7 [7.6–17.6])</td>
<td>0.43 (0.20–0.93)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pneumothorax — no. (% [95% CI])‡</td>
<td>7 (4.0 [2.0–8.0])</td>
<td>19 (11.7 [7.6–17.6])</td>
<td>0.34 (0.15–0.78)</td>
<td>0.01</td>
</tr>
<tr>
<td>MRC score — median (IQR)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 28</td>
<td>55 (46–60)</td>
<td>55 (39–60)</td>
<td></td>
<td>1.07 (0.80–1.45)</td>
</tr>
<tr>
<td>At ICU discharge</td>
<td>55 (43–60)</td>
<td>55 (44–60)</td>
<td></td>
<td>0.92 (0.71–1.19)</td>
</tr>
<tr>
<td>Patients without ICU-acquired paresis‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By day 28 — no./total no. (% [95% CI])</td>
<td>68/96 (70.8 [61.1–79.0])</td>
<td>52/77 (67.5 [56.5–77.0])</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>By ICU discharge — no./total no. (% [95% CI])</td>
<td>72/112 (64.3 [55.1–72.6])</td>
<td>61/89 (68.5 [58.3–77.3])</td>
<td>0.51</td>
<td></td>
</tr>
</tbody>
</table>
Context

Context of current care
Related trials
Criticisms of the trial
Incomplete Blinding

- Adequate blinding of caregivers implausible for some patients, particularly those with profound respiratory acidosis and air hunger
- In general, unblinded studies overestimate treatment effects

VALID CRITICISM; NOT A FATAL FLAW.
Lack of Monitoring

1. Depth of blockade
   - No peripheral nerve stimulation
   - Monitored $P_{plat}$

2. Ventilator dyssynchrony in the placebo group
   - Could inadequate monitoring and management of dyssynchrony in the placebo group predispose to worse outcomes?

VALID CRITICISM; NOT A FATAL FLAW.
Suitability of MRC Scale

• Assessed strength in 3 muscles groups in each arm and leg, at 28 days or ICU discharge
• Recovery period may be too brief to detect differences, particularly if patients slow to awaken
• 10% of live patients did not contribute data
• Future approach
  – More protracted MRC assessments
  – Electrophysiologic assessments

VALID CRITICISM; NOT A FATAL FLAW.
many clinicians are already paralyzing in severe ARDS
observational studies have rightly tempered our enthusiasm
an imperfect but methodologically strong RCT suggests a survival benefit, at no apparent increased risk of prolonged weakness
short-term neuromuscular blockade with cisatricurium for patients with severe ARDS (eg, PaO₂/FiO₂ ≤ 120) is probably safe and likely beneficial
further study is required to replicate these findings
Ideal NMB Agent

- rapid onset of paralysis
- titratable effect
- rapid offset, to allow neurologic assessments
- no adverse physiologic effects
- elimination independent of hepatic or renal function
- inactive metabolites
- modest cost
<table>
<thead>
<tr>
<th>agent</th>
<th>onset (min)</th>
<th>duration (min)</th>
<th>renal – hepatic</th>
<th>active metabolit</th>
<th>adverse effects</th>
<th>cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>pancuronium</td>
<td>3-6</td>
<td>90</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
<td>tachycardia</td>
<td>+</td>
</tr>
<tr>
<td>vecuronium</td>
<td>2-3</td>
<td>30-75</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>rocuronium</td>
<td>1.5-2</td>
<td>30-60</td>
<td>✓ ✓</td>
<td>✓</td>
<td>(tachycardia)</td>
<td>++</td>
</tr>
<tr>
<td>atricurium</td>
<td>2-3</td>
<td>30-60</td>
<td>✓ ✓ ✓</td>
<td></td>
<td>(CNS excitation) (hypotension)</td>
<td>+++</td>
</tr>
<tr>
<td>cisatricurium</td>
<td>2-3</td>
<td>45-60</td>
<td></td>
<td></td>
<td></td>
<td>++++</td>
</tr>
</tbody>
</table>
Supportive Care

- *sedation* and analgesia prior to paralysis
- supervise closely - ventilator *disconnects* can be fatal
- *suction* based on amount of secretions – (no cough reflex)
- *elevate* head of the bed to reduce aspiration, and VAP
- artificial *tears*, tape eyelids to prevent corneal ulceration
- frequent *turning* and dry bedding to prevent skin breakdown

- *enteral feeding* is not contraindicated!
Increased tidal volume secondary to increased respiratory drive due to:

- Arterial PO₂
- Lung reflectors
- Anxiety
- Permissive hypercapnia

"atelectrauma"

Dysfunction or organ failure due to:

- Arterial PO₂
- Blood flow
- ↑ Mediators

Te lungs

After paralysis

Respiratory cycle

- Patient: No pressure signal, No dysynchrony
- Pressure generated
- Ventilator: Lower tidal volume, Lower capillary permeability

Less ventilator-induced lung injury

- Less barotrauma
- Less injury due to ↓ pulmonary blood flow
- ↓ Venous PO₂
- Direct anti-inflammatory effect of NMBAs

Less inflammation

Mediators

O₂ molecules

Less translocated mediators from alveoli to bloodstream

Vital organs

Muscles