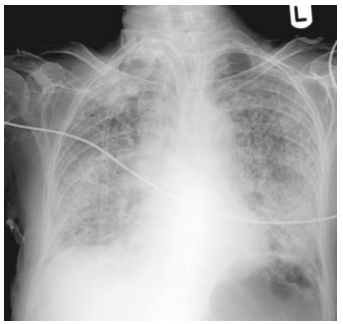
Neuromuscular Blockade in ARDS



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Disclosures

None

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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	**Potential harms**
Synchrony	Prolonged weakness
Oxygenation	Hemodynamics
Reduced VILI	Cost
Survival	

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)

Intensive Care Med (2001) 27: 1288–1296
DOI 10.1007/s001340101009

ORIGINAL

J. Garnacho-Montero

Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients

- 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

Mehta S, Burry L, et al. Crit Care Med. 2006;34(2):374.

- 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

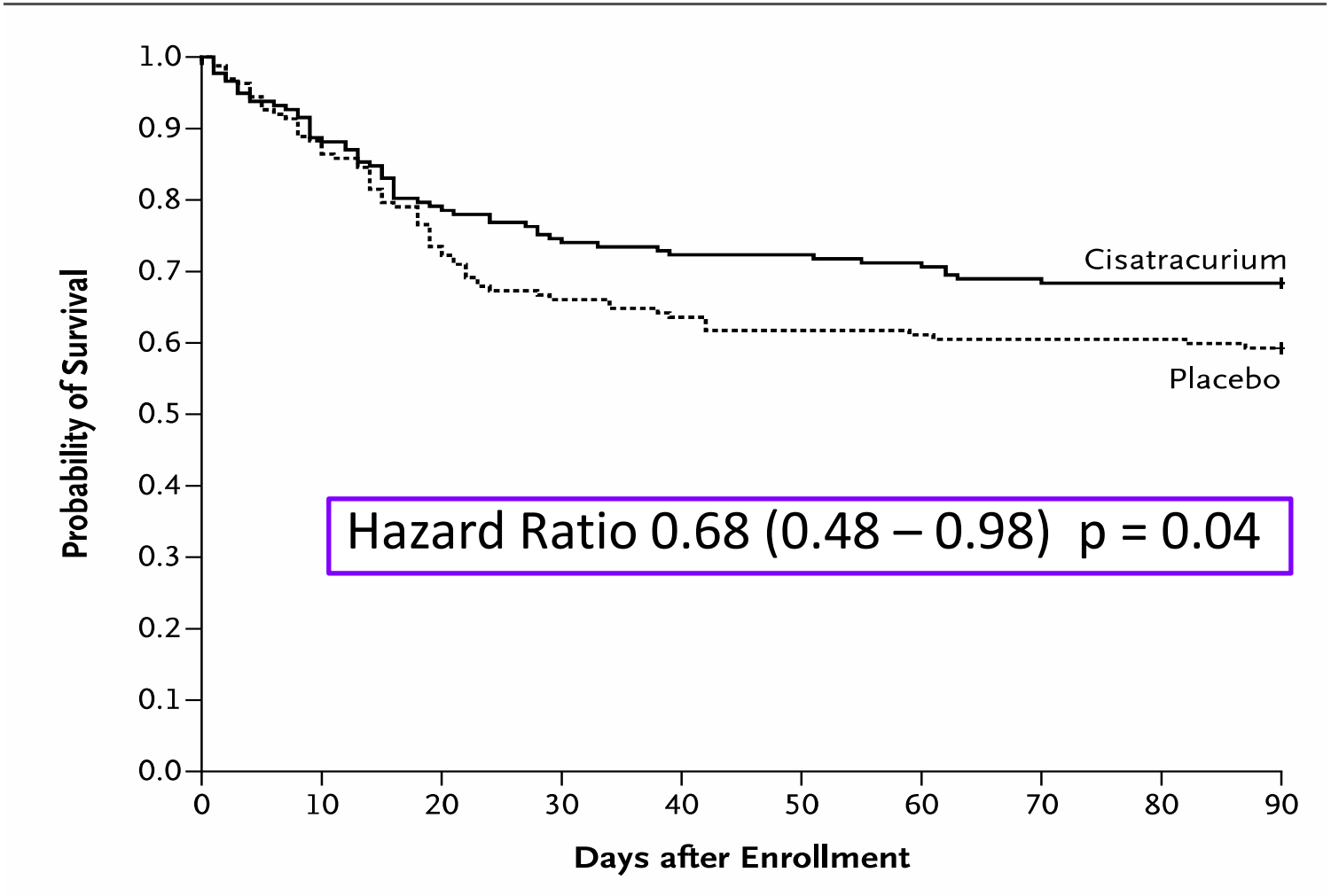
- OSCILLATE
  - (P/F ≤ 200)… 32.8% at baseline

- 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 $\geq$ 5 cm H_2O; 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 H_2O - no peripheral nerve stimulation
Analysis…	adjusted RR hospital mortality at 90 days (P/F, SAPS II, Pplat)

Mortality at 90 Days

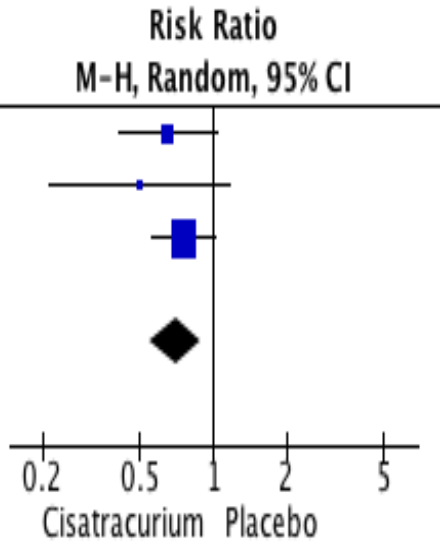


Meta-analysis: ICU Mortality

Study or Subgroup	Cisatracurium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Gainnier 2004	13	28	20	28	27.2%	0.65 [0.41, 1.03]	2004
Forel 2006	5	18	10	18	8.0%	0.50 [0.21, 1.17]	2006
papazian 2010	52	177	63	162	64.8%	0.76 [0.56, 1.02]	2010
Total (95% CI)		**223**		**208**	**100.0%**	**0.70 [0.55, 0.89]**	
Total events	70		93				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.95$, df = 2 (P = 0.62); $I^2 = 0\%$

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



With permission, Dr. Waleed Alhazzani

Table 3. Secondary Outcomes, According to Study Group.*

Outcome	Cisatracurium (N=177)	Placebo (N=162)	Relative Risk with Cisatracurium (95% CI)	P Value
Death — no. (% [95% CI])				
At 28 days	42 (23.7 [18.1–30.5])	54 (33.3 [26.5–40.9])	0.71 (0.51–1.00)	0.05
In the ICU	52 (29.4 [23.2–36.5])	63 (38.9 [31.7–46.6])	0.76 (0.56–1.02)	0.06
In the hospital	57 (32.2 [25.8–39.4])	67 (41.4 [34.1–49.1])	0.78 (0.59–1.03)	0.08
No. of ventilator-free days†				
From day 1 to day 28	10.6±9.7	8.5±9.4		0.04
From day 1 to day 90	53.1±35.8	44.6±37.5		0.03
No. of days without organ failure, from day 1 to day 28				
No cardiovascular failure	18.3±9.4	16.6±10.4		0.12
No coagulation abnormalities	22.6±8.9	20.5±9.9		0.05
No hepatic failure	21.3±9.6	19.1±10.6		0.05
No renal failure	20.5±10.1	18.1±11.6		0.05
None of the four	15.8±9.9	12.2±11.1		0.01
No. of days outside the ICU				
From day 1 to day 28	6.9±8.2	5.7±7.8		0.16
From day 1 to day 90	47.7±33.5	39.5±35.6		0.03
Hospital survivors admitted to other health care facilities from day 1 to day 90 — % (95% CI)	22.3 (15.8–30.5)	18.8 (12.2–27.8)		0.52
Barotrauma — no. (% [95% CI])‡	9 (5.1 [2.7–9.4])	19 (11.7 [7.6–17.6])	0.43 (0.20–0.93)	0.03
Pneumothorax — no. (% [95% CI])	7 (4.0 [2.0–8.0])	19 (11.7 [7.6–17.6])	0.34 (0.15–0.78)	0.01
MRC score — median (IQR)§				
At day 28	55 (46–60)	55 (39–60)	1.07 (0.80–1.45)	0.49
At ICU discharge	55 (43–60)	55 (44–60)	0.92 (0.71–1.19)	0.94
Patients without ICU-acquired paresis¶				
By day 28 — no./total no. (% [95% CI])	68/96 (70.8 [61.1–79.0])	52/77 (67.5 [56.5–77.0])		0.64
By ICU discharge — no./total no. (% [95% CI])	72/112 (64.3 [55.1–72.6])	61/89 (68.5 [58.3–77.3])		0.51

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 Pplat
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.

Summary

- 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, $PaO_2/FiO_2 \leq 120$) 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

agent	onset (min)	duration (min)	renal – hepatic	active metabolit	adverse effects	cost
pancuronium	3-6	90	✓✓✓	✓✓	tachycardia	+
vecuronium	2-3	30-75	✓✓	✓✓		++
rocuronium	1.5-2	30-60	✓✓	✓	(tachycardia)	++
atricurium	2-3	30-60	(✓)		(CNS excitation) (hypotension)	+++
cisatricurium	2-3	45-60				++++

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!

↑ Lung volume
Active expiration
↑ Lung volume
↑ Lung volume
↓ Lung volume
Increased tidal volume secondary to increased respiratory drive due to:
↓ Arterial PO2
Lung reflexes
Anxiety
Permissive hypercapnia
Volutrauma
"Atelectrauma"
Dysfunction or organ failure due to:
↓ Arterial PO2
↓ Blood flow
↑ Mediators
Vital organs
Muscles
To lungs
After paralysis
Less ventilator-induced lung injury
Respiratory cycle
Patient
No pressure signal
No dyssynchrony
↑ Pressure generated
Ventilator
Less barotrauma
↓ Injury due to ↓ pulmonary blood flow
↑ Lung volume
Lower tidal volume
↓ Mediators (e.g., interleukin-8)
Less biotrauma
O2 molecules
↑ Venous PO2
Direct anti-inflammatory effect of NMBA