

ORIGINAL ARTICLE

Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*

Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) Trial

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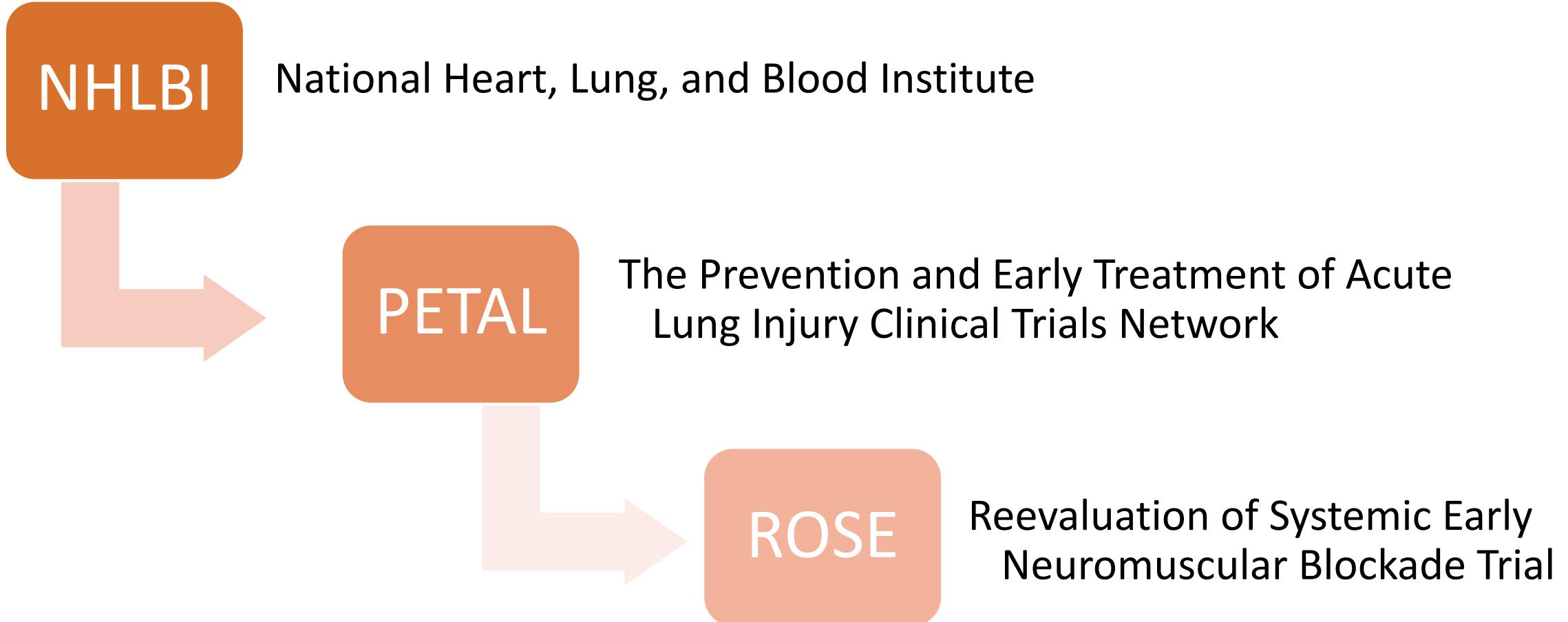


@DrTracieLin

Background

- It is well established that vent strategies can affect survival/outcome in ARDS
- Neuromuscular blockade (NMB)
 - Reduces patient-vent dyssynchrony
 - “ work of breathing
 - “ accumulation of alveolar fluid
 - When prolonged, is associated with subsequent neuromuscular weakness
- **ARDS et Curarisation Systematique (ACURASYS)**
 - Study done a decade ago
 - Early administration of NMB x 48 hrs with mod-severe ARDS ($P/F < 150$, $PEEP \geq 5$)
 - Result: Lower mortality (vs. deep sedation w/o NMB)
- Current ARDS guidelines: NMB only weakly recommended. Why?
 - Insufficient research comparing to current practice.
 - Limited data on effect of NMB on neuromuscular function and long-term outcomes.
 - NMB necessitates deeper sedation, which itself can have negative outcomes.

Background



Overview

Design	Multicenter RCT, unblinded inpatient, outpatient f/u blinded
P	<ul style="list-style-type: none">- Adults- Moderate-to-severe ARDS<ul style="list-style-type: none">- $\text{PaO}_2/\text{FiO}_2 < 150$ and PEEP ≥ 8- January 2016 to April 2018
I	Cis x 48 hrs + deep sedation
C	“Usual care” w/o routine NMB + lighter sedation
O	<u>Primary Outcome:</u> In-hospital death (all cause) at 90 days Trial stopped for futility. (No difference in mortality.)

Methods

- Designed to be consistent with some elements of the previous ACURASYS trial
 - Same NMB (cisatracurium), dosing regimen, and duration of treatment
 - Difference: Lighter sedation targets (c/w current practice recs)
- Mechanical ventilation protocol
 - High PEEP, low tidal volume, low plateau pressures
 - Recommended conservative fluid strategy
- Follow up interviews at 3, 6, and 12 months s/p randomization
 - Interviewers blinded to group assignment

Methods

- Patients:
 - Intubated Adults with ARDS at multiple US centers
 - $\text{PaO}_2/\text{FiO}_2 < 150$ with a $\text{PEEP} \geq 8 \text{ cmH}_2\text{O}$
 - If ABG not available, PaO_2 inferred from SpO_2
 - Bilateral pulmonary opacities (CXR or CT), not explained by effusions, pulmonary collapse, or nodules
 - Resp failure not explained by cardiac failure or fluid overload
- Randomization: 1:1

Methods

- Treatment:
 - For Intervention Group: Within 4 hrs of randomization, get to desired sedation level → bolus cis 15mg → cis gtt 37.5 mg/hr x 48 hrs
 - Note: Can d/c cis early if pt meets criteria for d/c mechanical ventilation, i.e. $\text{FiO}_2 \leq 0.4$ and $\text{PEEP} \leq 8$ x at least 12 hrs
 - For Control Group: “Light sedation” defined by one of the following:
 - Richmond Agitation-Sedation Scale of 0 or -1 (0 = Alert and calm)
 - Riker Sedation-Agitation Scale of 3 or 4 (4 = Calm and cooperative)
 - Ramsay Sedation Scale of 2 or 3 (2 = Cooperative and oriented)
 - All patients:
 - Within 2 hrs after randomization: Low tidal volume & high PEEP for up to 5 days
 - Note: Lower PEEP ok if:
 - Higher PEEP → worse oxygenation, hypotension, plateau $>30 \text{ cmH}_2\text{O}$, or acidemia ($\text{pH} < 7.15$)... despite ↓ tidal volume, fluid boluses, or increased RR
 - Or pneumothorax
 - Or high risk for barotrauma
 - Can prone at discretion of clinician

Statistical Analysis Highlights

- **Power analysis:**

For 90% power to reject the null hypothesis, at a 2-sided alpha level of 0.05...
and assuming that 27% of patients in intervention group and 35% in control
group would die (8 percentage point difference)...
Calculated that need to enroll **1408 patients**.

- All analyses performed by **intention-to-treat principle**

Baseline Characteristics

-Similar between groups

Patients enrolled at 7.6 hrs (IQR 3.7-15.6) after dx of mod-sev ARDS

→ Then time from enrollment to randomization: ~7-8 hrs (See table)

→ Then time from randomization to cis gtt (if Tx group): 1.9 ± 1.4 hrs

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Intervention Group (N=501)	Control Group (N=505)
Age — yr	56.6 ± 14.7	55.1 ± 15.9
Female sex — no. (%)†	210 (41.9)	236 (46.7)
White race — no. (%)†	361 (72.1)	344 (68.1)
Shock at baseline — no. (%)	276 (55.1)	309 (61.2)
Median time from enrollment to randomization (IQR) — hr	8.2 (4.0–16.4)	6.8 (3.3–14.5)
Neuromuscular blockade use between meeting inclusion criteria and randomization — no./total no. (%)	55/484 (11.4)	50/484 (10.3)
Primary cause of lung injury — no. (%)		
Pneumonia	292 (58.3)	301 (59.6)
Aspiration	91 (18.2)	75 (14.9)
Nonpulmonary sepsis	68 (13.6)	71 (14.1)
Other cause	50 (10.0)	58 (11.5)
Assessments and measurements		
APACHE III score‡	103.9 ± 30.1	104.9 ± 30.1
Total SOFA score§	8.7 ± 3.6	8.8 ± 3.6
Tidal volume — ml/kg of predicted body weight¶	6.3 ± 0.9	6.3 ± 0.9
$\text{FiO}_2\parallel$	0.8 ± 0.2	0.8 ± 0.2
Inspiratory plateau pressure — cm of water**	25.5 ± 6.0	25.7 ± 6.1
PEEP — cm of water††	12.6 ± 3.6	12.5 ± 3.6
$\text{Pao}_2:\text{FiO}_2$ — mm Hg‡‡	98.7 ± 27.9	99.5 ± 27.9
Imputed $\text{Pao}_2:\text{FiO}_2$ — mm Hg§§	94.8 ± 26.7	93.2 ± 28.9

Baseline Characteristics

-Similar between groups

Except: Shock at baseline — no. (%)

Patients enrolled at 7.6 hrs (IQR 3.7-15.6) after dx of mod-sev ARDS

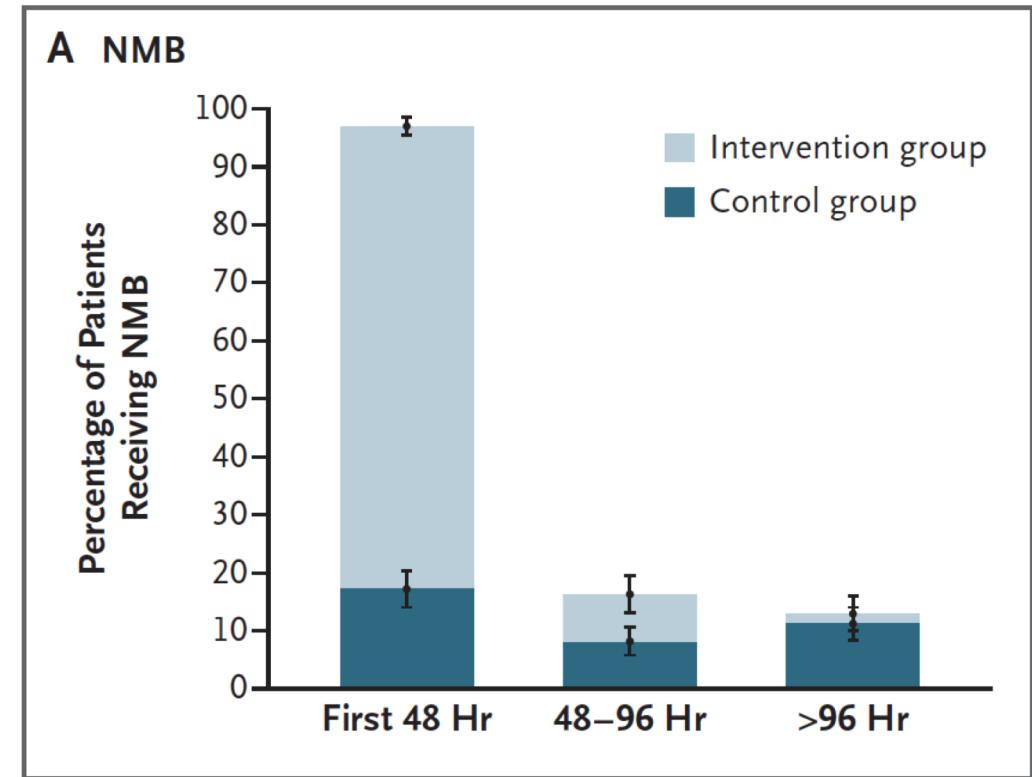
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Imputed Pao ₂ :F _i O ₂ — mm Hg§§	94.8 ± 26.7	93.2 ± 28.9	

Results: Did groups get intended treatment? **Mostly, Yes.**

- Intervention Group: 97.4% got cis gtt, x 47.8 hrs (IQR 43.8-48.0), median cumulative dose cis 1807 mg (IQR 1706-1815)
- Control Group: 17% got any cis, median cumulative dose cis 38 mg (IQR 14-200)
- In both groups, good adherence to mechanical ventilation protocol:
 - Low tidal volume: 80.1 – 87.5% adherence
 - Low plateau pressure: 85.6 – 90.8% adherence
 - No difference in median daily fluid balance b/t groups
 - Day 2: +327
 - Day 3: -242



Results

- Stopped at the 2nd interim analysis for futility. Decision made independently by data and safety monitoring board (DSMB). (n=1006 patients)
- Primary Outcome:

Variable	Intervention Group (N = 501)	Control Group (N = 505)	Between-Group Difference (95% CI)	P Value
<i>percentage points</i>				
Primary end point: in-hospital death by day 90 — no. (%)†	213 (42.5±2.2)	216 (42.8±2.2)	-0.3 (-6.4 to 5.9)	0.93

Note: Even by subgroup analysis (e.g. stratified by ARDS severity, ARDS duration, trial site's tercile of exclusion for prior NMB use), still no intervention vs. ctrl group difference.

- Secondary Outcomes:

- **Organ dysfunction (SOFA score):** Small difference in CV SOFA score day 1 only
- In-hospital mortality at 28 days
- Days free of organ dysfunction
- Days not in ICU
- Days free of mechanical ventilation
- Days not in hospital at day 28
- At 3, 6, and 12 months:
 - Survival
 - Disability
 - Health-related QOL
 - Cognitive function
 - Return to work
 - Patient-reported health
 - Pain interference
 - Symptoms resembling post-traumatic stress

- Secondary Outcomes:

- **Organ dysfunction (SOFA score):** Small difference in CV SOFA score day 1 only

Variables	SOFA Score				
	0	1	2	3	4
Respiratory	$\text{PaO}_2/\text{FiO}_2: > 400$ $\text{SpO}_2/\text{FiO}_2: > 302$	$\text{PaO}_2/\text{FiO}_2: < 400$ $\text{SpO}_2/\text{FiO}_2: < 302$	$\text{PaO}_2/\text{FiO}_2: < 300$ $\text{SpO}_2/\text{FiO}_2: < 221$	$\text{PaO}_2/\text{FiO}_2: < 200$ $\text{SpO}_2/\text{FiO}_2: < 142$	$\text{PaO}_2/\text{FiO}_2: < 100$ $\text{SpO}_2/\text{FiO}_2: < 67$
Cardiovascular (doses in mcg/kg/min)	$\text{MAP} \geq 70 \text{ mm Hg}$	$\text{MAP} \geq 70 \text{ mm Hg}$	Dopamine ≤ 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine > 15 or Norepinephrine > 0.1 Phenylephrine > 0.8
Liver (bilirubin, mg/dL)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12
Renal (creatinine, mg/dL)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
Coagulation (platelets $\times 10^3/\text{mm}^3$)	≥ 150	< 150	< 100	< 50	< 20
Neurologic (GCS score)	15	13-14	10-12	6-9	< 6

- Symptoms resembling post-traumatic stress

- Secondary Outcomes:

- Organ dysfunction (SOFA score): Small difference in CV SOFA score day 1 only

Variables	SOFA Score
0	0
1	1
2	2
3	3
4	4

Table S24. Safety measures observed during the 6 hours after randomization

Characteristic	Intervention (N=501)	Control (N=505)	Difference (95% CI)
Fluid bolus given - % yes	16.4	14.7	1.7 (-2.8, 6.2)
Vasopressors started or increased - % yes	45.9	36.6	9.3 (3.2, 15.3)
Fluid intake	1161 ± 1170 (n=498)	1101 ± 1089 (n=502)	60 (-80, 201)
Fluid output	519 ± 666 (n=495)	545 ± 665 (n=498)	-25 (-108, 57)

Plus-minus values are means ± SD.

(GCS score)

- Symptoms resembling post-traumatic stress

- Safety Endpoints:

- Recall of paralysis (Modified Brice questionnaire)
- **ICU-acquired weakness up to day 28**
(Medical Research Council Scale: Scores from 0-5 for muscle strength in 6 muscle groups x 2 sides of body)
- Limitations on physical activity
(ICU Mobility Scale: Scores from 0 [no movement] to 10 [walking w/o aid])
- New onset atrial fibrillation or SVT
- Barotrauma
- **Investigator-reported adverse events**

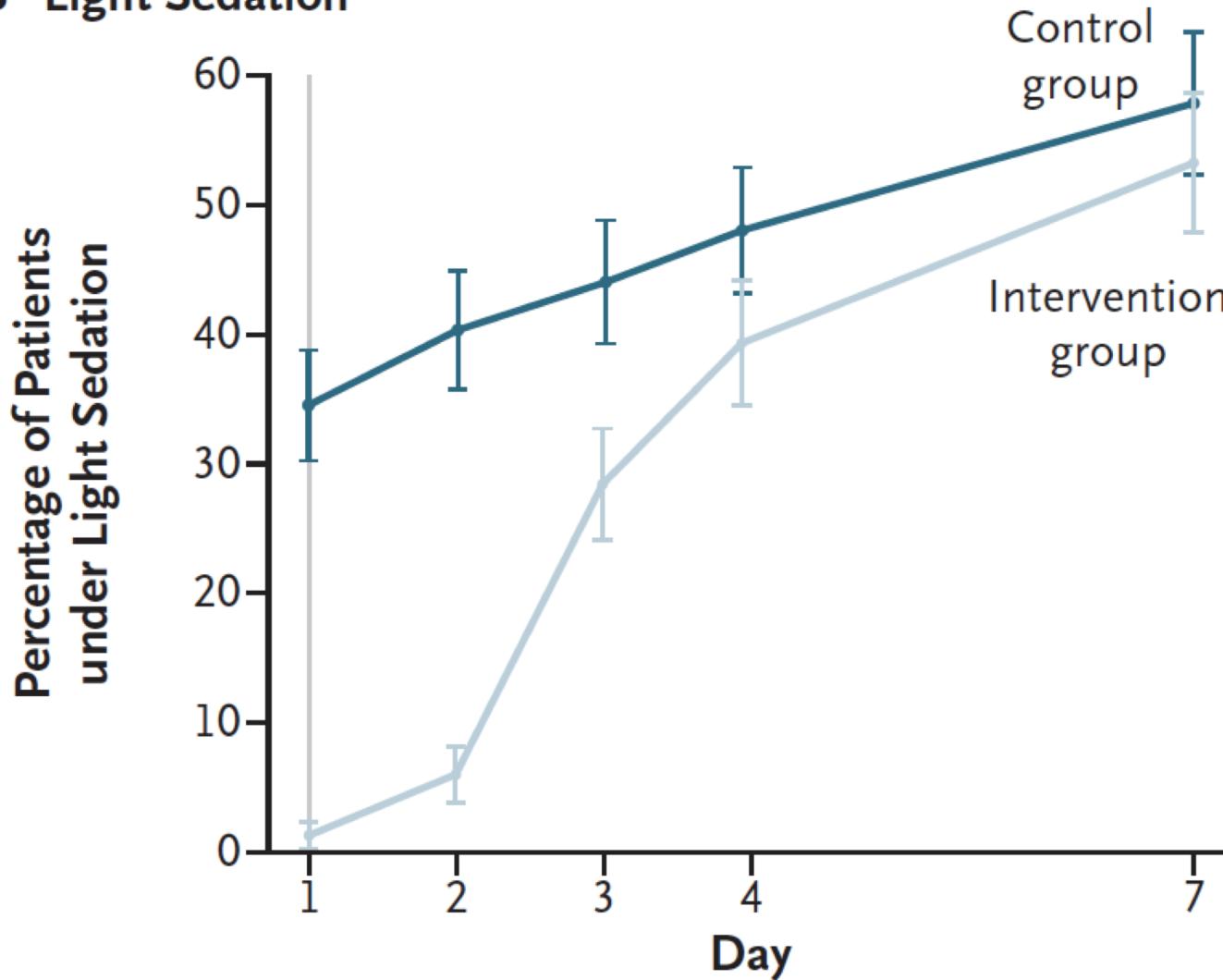
	Intervention	Control.	Between Group diff (95% CI)
ICU-acquired weakness — no./total no. (%) 			
Day 7	50/122 (41.0)	41/131 (31.3)	-9.7 (-21.5 to 2.1)
Day 28	22/47 (46.8)	14/51 (27.5)	-19.4 (-38.2 to -0.6)
Any time through day 28	107/226 (47.3)	89/228 (39.0)	-7.3 (-15.7 to 1.1)
Serious adverse events — no. of events**	35	22	0.09
Serious cardiovascular adverse events — no. of events**	14	4	0.02



Table S25. Adverse events by organ system, event and severity

System/disorder	Event	Severity	Intervention	Control	Overall	P-value
Blood/lymphatic	Methemoglobinemia	Serious	2	0	2	0.16
Cardiac	Complete atrioventricular block	Serious	1	0	1	0.32
	Atrial fibrillation (paroxysmal)	Non-Serious	1	0	1	0.32
	Atrial fibrillation w/ rapid vent response	Serious	1	0	1	0.32
	Bradycardia	Serious	1	0	1	0.18
		Non-Serious	1	0	1	
	Cardiac arrest	Serious	6	2	8	0.3
		Non-Serious	0	2	2	
	Cardiac arrhythmia (NOS)	Non-Serious	1	0	1	0.32
	3rd degree atrioventricular block	Serious	0	1	1	0.32
	Myocardial infarction	Serious	1	1	2	1.0
	Serious prolonged bradycardia	Non-Serious	1	0	1	0.32
	Tachycardia	Non-Serious	1	0	1	0.32
	Supraventricular tachycardia	Serious	1	0	1	0.32
	Torsades De Pointe	Serious	1	0	1	0.32
	Vasovagal reaction	Non-Serious	0	1	1	0.32
	Ventricular tachycardia	Serious	2	0	2	0.16

B Light Sedation



Patients in the intervention (cis) group were more likely to be heavily sedated, even after the initial 48 hr period was over.

→ Possible effect on their outcomes?

“Results” that were not target end points:

- Differences between intervention vs. control groups
 - Intervention group had **lower PEEP** requirement, in first 24 hrs
(Between-group difference of -0.9 cmH₂O, CI -1.5-0.4)
 - Intervention group had **lower minute ventilation**, in first 48 hrs
(Between group difference of -0.7 LPM (CI -1.1 to -0.2) day 1, then -0.8 LPM (CI -1.2 to -0.4) day 2)
 - Intervention group had **lower FiO₂ requirement**, in first 48 hrs
(Between group difference of -0.04, CI -0.06 to -0.02)
 - Intervention group had **higher driving pressure** (Plateau-PEEP), in first 48 hrs
(Between group difference of 0.7 cmH₂O (CI 0.0 to 1.3) day 1, 0.8 cmH₂O (CI 0.1 to -1.5) day 2)
- **No difference** in PaO₂/FiO₂ from day 1 to day 7.

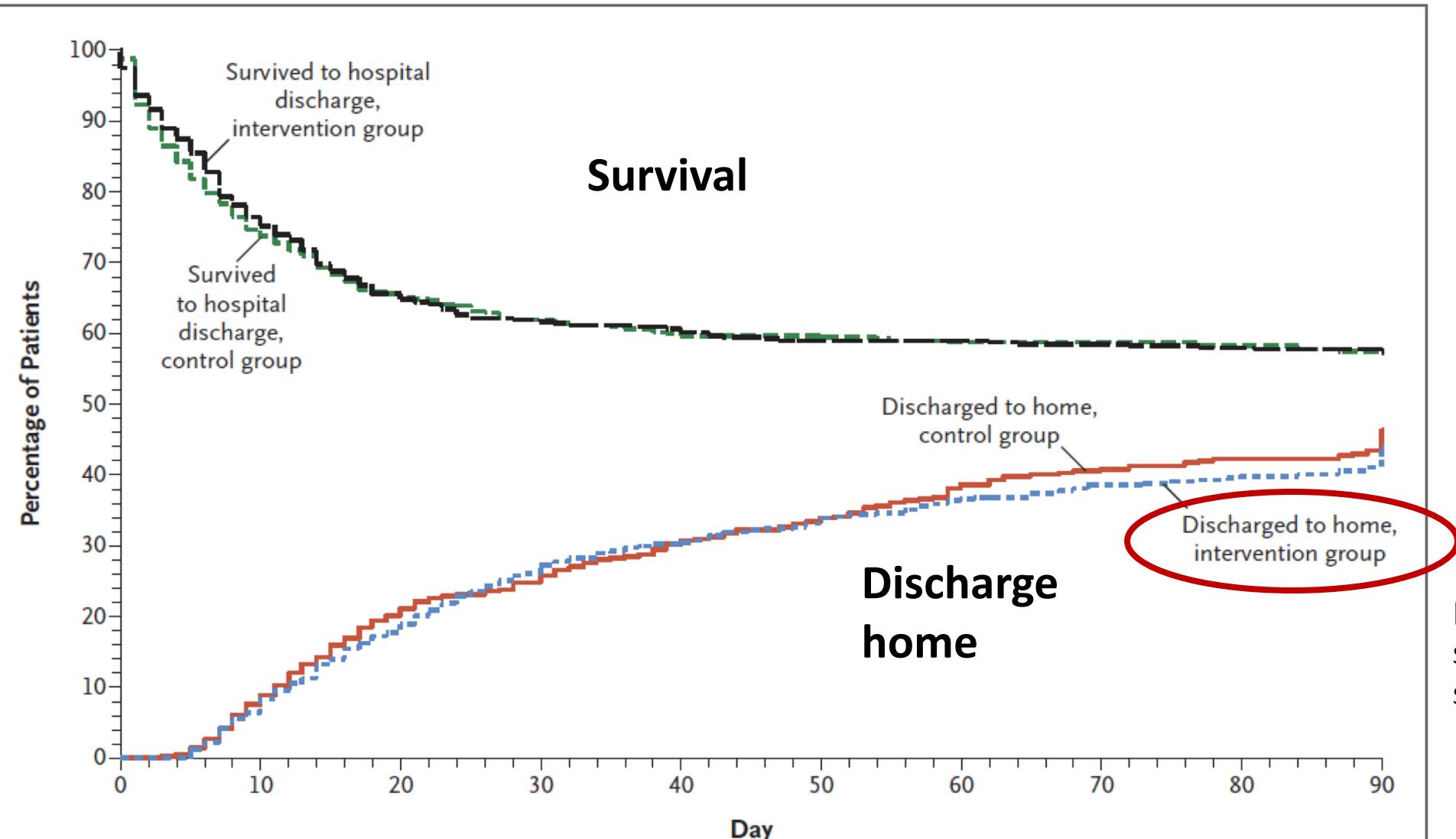


Figure 3. Patients Who Survived to Hospital Discharge and Were Discharged Home during the First 90 Days after Randomization.

The period of hospitalization included transfer to other health care facilities.

Limitations

- No train-of-four?!
 - “We chose not to adjust the dose of the NMB agent according to peripheral nerve stimulation both to replicate the dosing regimen used in the ACURASYS trial and to facilitate adherence to the trial protocol.”
- No subgroup analysis for prone positioning (Inadequate power?)
 - But prone positioning comparable between groups (~15%)
 - Paralytic use slightly overrepresented in proned (vs. supine) control group patients (44%)
- Top reason patients excluded: Use of NMB prior to enrollment. So were the patients left in the study the ones less likely to benefit from NMB?
 - But site-based sub-analyses were not suggestive of this being the case
- In-hospital assessments not blinded
→ May bias reporting of physical activity and adverse events?

ROSE Trial -- Take Home Points

- NMB x 48 hrs early in (adult) ARDS: **No mortality benefit**
- **Potential harm?**
 - NMB → ↑ sedation during and after NMB → sedation med sequelae, ↓ physical activity later, increase in CV events → (trend towards) less likely d/c to home
- **Short-term benefits** of NMB:
 - PEEP lower (by approx. 1 cmH₂O)
 - Marginally lower FiO₂ requirement (by 4% FiO₂)

- **Why was result different than in ACURASYS?** Hypotheses:
 - Higher PEEP strategy → better survival for all → blunt potential tx effect of NMB?
 - Control group was more lightly sedated (In ACURASYS, all pts deeply sedated) → improved outcomes?
 - Proning similar between ROSE study groups, but ROSE had a smaller percentage of patients prone than ACURASYS

Thanks

Supplemental Slides

End Points

Table 2. End Points.*

Variable	Intervention Group (N=501)	Control Group (N=505)	Between-Group Difference (95% CI)	P Value
<i>percentage points</i>				
Primary end point: in-hospital death by day 90 — no. (%)†	213 (42.5±2.2)	216 (42.8±2.2)	-0.3 (-6.4 to 5.9)	0.93
Secondary end points				
In-hospital death by day 28 — no. (%)	184 (36.7)	187 (37.0)	-0.3 (-6.3 to 5.7)	
Days free of ventilation at day 28‡	9.6±10.4	9.9±10.9	-0.3 (-1.7 to 1.0)	
Days not in ICU at day 28	9.0±9.4	9.4±9.8	-0.4 (-1.6 to 0.8)	
Days not in hospital at day 28‡	5.7±7.8	5.9±8.1	-0.2 (-1.1 to 0.8)	
Safety end points				
In-hospital recall of paralysis				
Total no. of patients (%)	9 (1.8)	10 (2.0)	-0.2 (-1.9 to 1.5)	
Among patients who received neuromuscular blockade — no./total no. (%)	9/487 (1.8)	2/129 (1.6)	0.3 (-2.1 to 2.7)	
MRC score§				
Day 7	46.7±14.4	49.5±12.3	-2.8 (-6.1 to 0.6)¶	
Day 28	45.7±13.9	49.8±10.6	-4.1 (-9.0 to 0.9)¶	
ICU-acquired weakness — no./total no. (%)				
Day 7	50/122 (41.0)	41/131 (31.3)	-9.7 (-21.5 to 2.1)	
Day 28	22/47 (46.8)	14/51 (27.5)	-19.4 (-38.2 to -0.6)	
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Serious adverse events — no. of events**	35	22		0.09
Serious cardiovascular adverse events — no. of events**	14	4		0.02
Atrial fibrillation or SVT during ICU stay — no. (%)	101 (20.2)	99 (19.6)		0.88
Barotrauma — no. (%)	20 (4.0)	32 (6.3)		0.12
Pneumothorax on days 0 through 2 — no. (%)	8 (1.6)	10 (2.0)		0.81
Pneumothorax on days 0 through 7 — no. (%)	14 (2.8)	25 (5.0)		0.10

Table S1. Additional baseline characteristics

Characteristic	Intervention (N=501)	Control (N=505)
Black- no. (%)	63 (12.6)	79 (15.6)
Hispanic or Latino- no. (%)	64 (12.8)	54 (10.7)
PaCO ₂ - mm Hg	44.1 ± 10.2 (n=470)	43.8 ± 12.0 (n=474)
Minute ventilation - L/min	11.3 ± 3.2 (n=469)	11.3 ± 3.7 (n=468)
Medical ICU - no. (%)	327 (65.3)	352 (69.7)
Primary cause of lung injury - no. (%)		
Trauma	16 (3.2)	23 (4.6)
Multiple transfusion	13 (2.6)	7 (1.4)

Plus-minus values are means ± SD with (no.). Race and ethnicity was assigned by the coordinators on the basis of hospital records or information from the next of kin. PaCO₂ denotes the partial pressure of arterial carbon dioxide. ICU denotes intensive care unit.

Table S14. Day 90 mortality percentage estimates stratified by ethnicity

Characteristic	Intervention	Control	Difference (95% CI)	P-value
Hispanic or Latino (N=118)	32.8 ± 5.9 (64)	53.7 ± 6.8 (54)	-20.9 (-38.5, -3.3)	
Not Hispanic or Latino (N=831)	44.6 ± 2.5 (410)	42.0 ± 2.4 (421)	2.6 (-4.1, 9.3)	
Interaction			-23.5 (-42.3, -4.7)	0.015

Mortality percentage - (# of patients who died/# of patients enrolled) x 100 ± StdErr (no.). P-value is calculated from Wald test.