Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

Supplementary Materials

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Supplementary methods

Trial design and oversight

Trial data were collected by the PETAL network investigators, monitored by the PETAL clinical coordinating center, and analyzed by the authors, who drafted the manuscript and vouch for the accuracy and completeness of the analyses and for the fidelity of the trial to the protocol. All authors made the decision to submit the manuscript for publication. The randomization to 48-hour continuous infusion of cisatracurium with concomitant deep sedation (intervention group) or to a usual care approach of lighter sedation targets (control group) obviated the ability for providers and bedside research staff to be blinded to the intervention assignment.

Inclusion criteria additional explanation

We selected our hypoxemia inclusion criterion to ensure a non-transient hypoxemia that persisted despite elevated positive end expiratory pressure (PEEP). The hypoxemia criterion was adjusted for the sites at an altitude of greater than 1000 meters (Denver, CO and Salt Lake City, UT). The PaO_2/FIO_2 criterion of 150 mmHg with PEEP ≥8 cmH_2O was multiplied by the ambient barometric pressure divided by sea level barometric pressure. The onset of illness was defined as within one week of a known clinical insult or new or worsening respiratory symptoms. If an arterial blood gas analysis was unavailable, an initial analysis in which the PaO_2 was inferred from the oxygen saturation measured by pulse oximetry (SpO_2) was used to estimate the PaO_2/FIO_2 ratio at PEEP ≥8 cmH_2O. An inferred PaO_2/FIO_2 <150 mmHg, if confirmed by a second assessment using SpO_2 1-6 hours later could be used to fulfill the hypoxemia criterion.

Exclusion criteria

1. Lack of informed consent
2. Continuous neuromuscular blockade (NMB) at enrollment (>2 NMB boluses excluding NMB given for reasons other than ARDS management [e.g., intubation or transport] or >3h continuous infusion)
3. Known pregnancy
4. Currently receiving extracorporeal membrane oxygenation therapy
5. Chronic respiratory failure defined as $PaCO_2$ >60 mmHg in the outpatient setting
6. Home mechanical ventilation (non-invasive or via tracheotomy) except for continuous or bilevel positive airway pressure support used solely for sleep-disordered breathing
7. Actual body weight exceeding 1 kg per centimeter of height
8. Severe chronic liver disease defined as a Child-Pugh score of 12-15
9. Bone marrow transplantation within the last year
10. Expected duration of mechanical ventilation <48 hours
11. Decision to withhold life-sustaining treatment, not including those patients committed to full support except cardiopulmonary resuscitation
12. Moribund patient not expected to survive 24 hours; if cardiopulmonary resuscitation (CPR) provided, assess for moribund status ≥6 hours from CPR conclusion
13. Diffuse alveolar hemorrhage from vasculitis
14. Burns >70% of total body surface
15. Unwillingness to utilize the NHLBI Acute Respiratory Distress Network (ARDS) Network 6 ml/kg ideal body weight ventilation protocol
16. Previous hypersensitivity or anaphylactic reaction to cisatracurium
17. Neuromuscular conditions that may potentiate NMB or impair spontaneous ventilation (study protocol, appendix A2)
18. Neurologic conditions undergoing treatment for intracranial hypertension
19. Enrollment in an interventional ARDS trial with direct impact on neuromuscular blockade and PEEP
20. Pa O_2/FIO_2 (if available) >200 mmHg after meeting inclusion criteria and before randomization
21. Endotracheal ventilation for greater than 120 hours (5 days)
22. Patient has completed lung transplant evaluation and has been officially listed for lung transplant by the United Network for Organ Sharing organization

Additional methods

1. The randomization used a permuted block design stratified by site.
2. Before implementing initial changes to PEEP, a PETAL investigator or designee determined hemodynamic appropriateness using the following criteria: mean arterial pressure >55 mmHg or systolic blood pressure >80 mmHg, and no fluid bolus or increase in vasopressor dosing for greater than 15 minutes. If hypotension occurred with the increase in PEEP, the protocol (study protocol, page 25) recommended the administration of a fluid bolus.
3. During shock, fluid management was unrestricted; and a simplified fluid conservative approach was recommended for those patients without shock (study protocol, page 54). A version of the protocolized NHLBI ARDS Network weaning strategy was also utilized (study protocol, pages 51-53).
4. All sites used the sedation scales with which clinical staff were already trained to administer as part of routine care. There were 3 scales used across sites: the Richmond Agitation-Sedation Score (RASS), the Riker Sedation Agitation Scale, and the Ramsay Sedation Scale.[1-3] RASS ranges from +4 (combative) to -5 (unarousable)], Riker from 1 (unarousable) to 7 (dangerous agitation), and Ramsay from 1 (anxious/restless) to 6 (unresponsive).
5. Before initiating neuromuscular blockade, study staff ensured (and documented) deep sedation defined as a RASS score of -5 [range: +4 (combative) to -5 (unarousable)], a Riker Sedation Agitation Scale score of 1-2 [range: 1 (unarousable) to 7 (dangerous agitation), where 2 equals very sedated], or a Ramsay Sedation Scale score of 5-6 [range: 1 (anxious/restless) to 6 (unresponsive), where 5 equals a sluggish response to stimulus]. Staff also ensured patients were receiving controlled modes of mechanical ventilation. We did not mandate sedative type or dose. Initiation of neuromuscular blockade began within 4 hours of randomization.
6. We allowed an open-label intravenous bolus injection of 20 mg of cisatracurium in both groups if the end-inspiratory plateau pressure remained greater than 30 cm of water for at least 10 minutes despite the administration of increasing doses of sedatives and decreasing the tidal volume and PEEP. If the neuromuscular blockade reduced the end-inspiratory plateau pressure by less than 2 cmH_2O, the protocol recommended a second 20 mg bolus of cisatracurium. If after the initial bolus, the end-inspiratory plateau pressure did not decrease by at least 2 cmH_2O, the protocol recommended that a bolus injection of cisatracurium should not be administered again during the following 24-hour period.
7. In the control group and in the intervention group after neuromuscular blockade had been withdrawn, light sedation targets were a RASS score of 0 to -1, a Riker score of 3 to 4, or a Ramsay score of 2-3.

Additional outcome measures

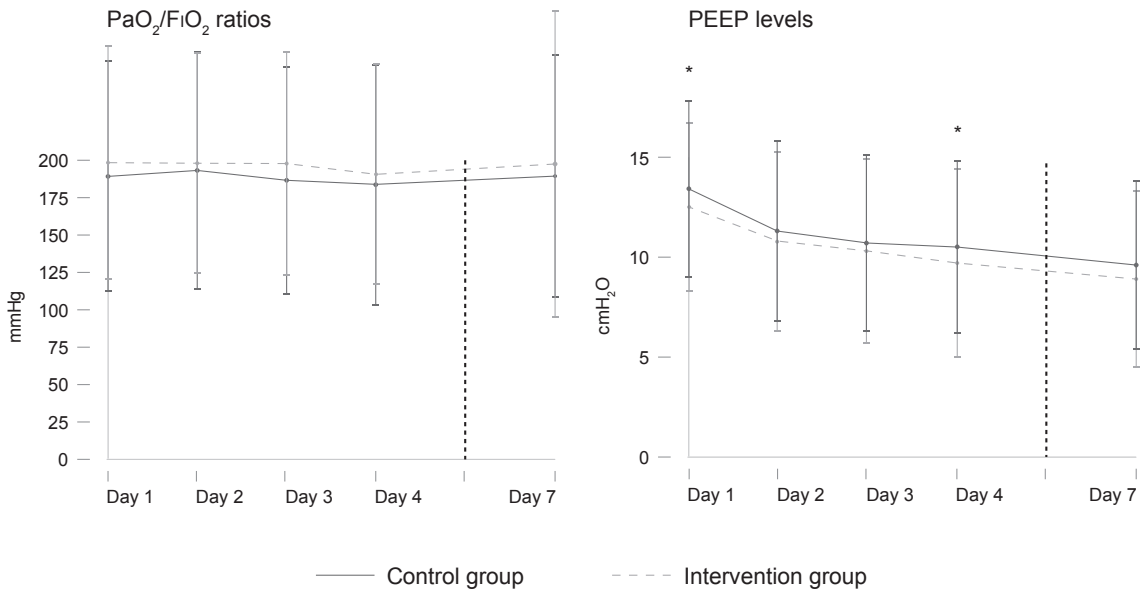
Intensive Care Unit (ICU)-acquired weakness was defined as a Medical Research Council (MRC) score of <48 (or mean MRC <4 when at least 7 of the 12 muscle group were tested).[4]

In addition, the following long-term outcome measures were obtained: a.) disability using Katz Activities of Daily Living (ADL)/Lawton Instrumental Activities of Daily Living Scale (IADL) plus two additional Nagi items, b.) health-related quality of life using the EuroQol (EQ-5D-5L), c.) self-rated health, d.) pain interference, e.) post-traumatic stress-like symptoms using the Post-Traumatic Stress Symptoms (PTSS14), f.) cognitive function using the Montreal Cognitive Assessment (MoCA-Blind) or, via proxy, the Alzheimer's Disease 8 (AD8) questionnaire, g.) ability to return to work, h.) subsequent hospital and emergency department use, and i.) location of residence.[5-9]

To avoid delay in publication of the primary results, we chose not to measure serum interleukin 6 concentrations, an additional outcome specified in the study protocol, before submission of this manuscript.

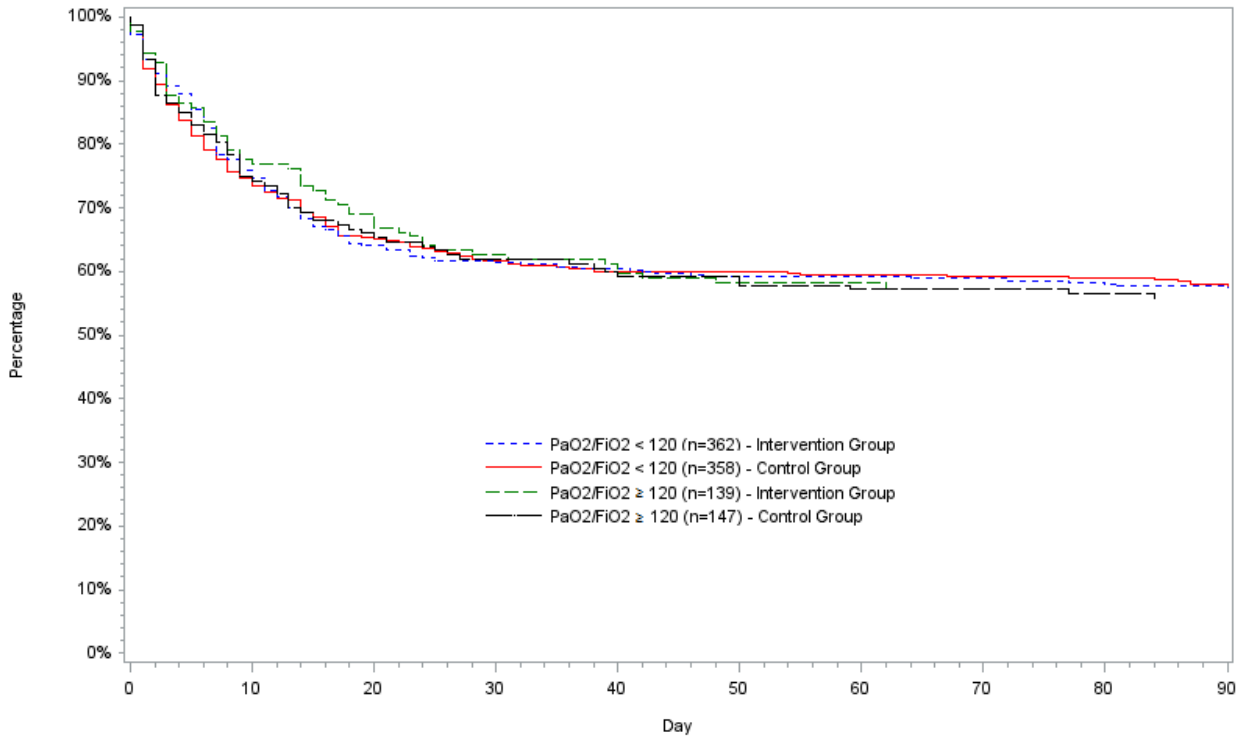
Supplementary figures

Figure S1. PaO_2/FIO_2 ratios and PEEP levels during the first week



Data displayed as means ± standard deviations. PaO_2 denotes partial pressure of arterial oxygen, FIO_2 denotes the fraction of inspired oxygen, PaO_2/FIO_2 ratios expressed as mmHg, PEEP denotes positive end-expiratory pressure and expressed as cmH_2O. Left panel: there were no differences in daily PaO_2/FIO_2 ratios between the intervention and control groups. Right panel: there were differences in PEEP levels between the intervention and control groups on days 1 and 4. Day 1 difference and 95% CI: -0.95 (-1.50, -0.41) and day 4 difference and 95% CI: -0.81 (-1.47, -0.15). See Table S5 for more details.

Figure S2. Survival curves for the subgroups, PaO_2/FiO_2 <120 and ≥120 mmHg



PaO_2 denotes partial pressure of arterial oxygen, FiO_2 denotes the fraction of inspired oxygen, and PaO_2/FiO_2 ratios expressed as mmHg. Data generated from Kaplan-Meier survival analysis, defining death as deaths occurring in-hospital, as per the primary outcome definition (see Methods). The cutoff values of <120 and ≥120 mmHg were pre-specified, based on a similar subgroup analysis in the ACURASYS study.[10] There was no interaction between treatment assignment and subgroup (p=0.76, see Table S9).

Supplementary tables

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. $PaCO_2$ denotes the partial pressure of arterial carbon dioxide. ICU denotes intensive care unit.

Table S2. Comparison of patients enrolled by a qualifying PaO_2/FIO_2 ratio or SpO_2/FIO_2 ratios

Characteristic	Intervention (N=501)	Control (N=505)
Qualifying PaO_2/FIO_2 (mmHg)	98.7 ± 27.9 (n=452)	99.5 ± 27.9 (n=460)
Imputed PaO_2/FIO_2 from SpO_2/FIO_2 (mmHg)	94.8 ± 26.7 (n=49)	93.2 ± 28.9 (n=45)
PEEP at time of qualifying PaO_2/FIO_2 (cmH_2O)	11.3 ± 3.2 (n=452)	11.3 ± 3.5 (n=460)
PEEP at time of qualifying SpO_2/FIO_2 (cmH_2O)	10.7 ± 2.9 (n=49)	9.8 ± 2.0 (n=45)

Plus-minus values are means ± SD with (no.). PaO_2 denotes partial pressure of arterial oxygen, FIO_2 denotes the fraction of inspired oxygen, SpO_2 denotes arterial oxygen saturation, and PEEP denotes positive end-expiratory pressure. Please see Supplementary Methods (page 5) and Study Protocol (page 44) for more information concerning the imputed PaO_2/FIO_2 calculations.

Table S3. Cisatracurium drug dosing information

Characteristic	Intervention (N=501)	Control (N=505)	Difference (95% CI)
Vasopressor adjustment during first 6 hours - no. (%)	230 (45.9)	185 (36.6)	9.3% (3.2, 15.3)
Fluid bolus during first 6 hours - no. (%)	82 (16.4)	74 (14.7)	1.7% (-2.8, 6.2)
Either of the above 2 interventions - no. (%)	254 (50.7)	214 (42.4)	8.3% (2.2, 14.5)
Had loading dose * - no. (%)	478 (95.4)	-	-
Had infusion started * - no. (%)	488 (97.4)	-	-
Additional bolus given - no. (%)	15 (3.3) (n=456)	-	-
Number of additional boluses	1.4 ± 0.8 (n=15)	-	-
Additional cisatracurium by bolus - mg	27.7 ± 16.4 (n=15)	-	-
Completed 48-hour Infusion ◊ - no. (%)	336 (74.5) (n=451)	-	-
Actual infusion time † ≥48.5 hours - no. (%)	9 (2.0) (n=451)	-	-
Infusion held - no. (%)	18 (4.0) (n=456)	-	-
Hold hours	6.4 ± 7.1 (n=18)	-	-
Infusion rate increased - no. (%)	4 (0.9) (n=456)	-	-
Maximum increased infusion rate - mg/hour	44.1 ± 7.5 (n=4)	-	-
Other NMB first 48 hours - no. (%)	4 (0.9) (n=456)	86 (17.0) (n=505)	-
Volume of other NMB first 48 hours - mg	83.4 ± 80.2 (n=4)	173.3 ± 285.3 (n=86)	-
Any NMB second 48 hours - no. (%)	73 (16.0) (n=456)	40 (7.9) (n=505)	-
Any NMB second 48 hours - mg	522.3 ± 536.2 (n=73)	355.8 ± 494.9 (n=40)	-
Any NMB after 2nd 48 hours - no. (%)	58 (12.7) (n=456)	57 (11.3)	-
Total cisatracurium during first 48 hours - mg	1806.9 ± 108.1 (n=451)	-	-
Cisatracurium stopped early - no. yes (% yes)	185 (45.7) (n=405)	-	-
Reason for early cisatracurium stopping - no. (%)	(n=185)		-
Met stopping allowance criteria	74 (40.0)	-	
Dose completed	48 (25.9)	-	
Death	27 (14.6)	-	
Other	20 (10.8)	-	
Unintentional early stop	13 (7.0)	-	
Adverse event	3 (1.6)	-	

Plus-minus values are means ± SD. NMB denotes neuromuscular blockade.

* Tabulation among patients who were randomized to the NMB arm

◊ Actual infusion time >45.6 hours

† Actual infusion time = infusion stop time - start time - hold duration

Table S4. Daily 'on study' sedation parameters from baseline through study day 7

Study day	Richmond Agitation-Sedation Score			Riker Sedation Agitation Scale		
	Intervention	Control	Difference (95% CI)	Intervention	Control	Difference (95% CI)
Baseline	-3.2 ± 7.0 (407)	-2.6 ± 1.8 (406)	-	2.3 ± 1.1 (79)	2.4 ± 1.1 (79)	-
Day 1	-4.8 ± 0.8 (395)	-2.7 ± 1.9 (402)	-2.1 (-2.3, -1.9)	1.1 ± 0.4 (76)	2.4 ± 1.3 (73)	-1.3 (-1.6, -1.0)
Day 2	- 4.6 ± 5.1 (376)	-2.3 ± 2.0 (372)	-2.3 (-2.9, -1.8)	1.3 ± 0.9 (75)	2.7 ± 1.3 (70)	-1.4 (-1.8, -1.1)
Day 3	-2.9 ± 2.0 (361)	-2.2 ± 2.0 (349)	-0.7 (-1.0, -0.4)	2.4 ± 1.3 (68)	2.9 ± 1.3 (65)	-0.5 (-1.0, -0.1)
Day 4	-2.7 ± 5.6 (341)	- 2.0 ± 2.0 (332)	-0.7 (-1.4, -0.1)	2.9 ± 1.3 (60)	2.8 ± 1.3 (62)	0.0 (-0.4, 0.5)
Day 5	-2.2 ± 2.0 (326)	-1.8 ± 2.0 (310)	-0.4 (-0.7, -0.1)	2.9 ± 1.3 (59)	2.9 ± 1.2 (57)	0.0 (-0.5, 0.5)
Day 6	-2.0 ± 2.0 (302)	-1.6 ± 2.0 (291)	-0.5 (-0.8, -0.2)	1.0 ± 13.9 (54)	3.1 ± 1.2 (51)	-2.1 (-6.0, 1.8)
Day 7	-1.6 ± 2.1 (280)	-1.5 ± 1.9 (257)	-0.1 (-0.4, 0.3)	3.3 ± 1.5 (46)	3.1 ± 1.5 (50)	0.2 (-0.4, 0.8)

Plus-minus values are means ± SD with (no).

Richmond Agitation-Sedation Score with a range: +4 (combative) to -5 (unarousable), where 0 equals alert and calm.[1] Riker Sedation Agitation Scale with a range: 1 (unarousable) to 7 (dangerous agitation), where 4 equals calm and cooperative]).[2] Only 2 patients were managed with the Ramsay scale.

Table S5. Ventilator and patient physiological parameters over time

	Baseline		Day 1		Day 2		Day 3		Day 4		Day 7	
Criteria	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Tidal volume *	6.3 ± 0.9 (445)	6.3 ± 0.9 (443)	5.9 ± 0.8 (457)	5.9 ± 0.7 (428)	5.9 ± 0.8 (425)	6.0 ± 0.8 (377)	5.9 ± 0.8 (366)	6.0 ± 0.8 (303)	6.0 ± 0.9 (304)	6.0 ± 0.7 (262)	6.1 ± 0.8 (164)	6.1 ± 0.9 (148)
Set rate ◊	23.8 ± 6.4 (485)	24.5 ± 6.7 (486)	27.3 ± 6.3 (479)	26.3[I] ± 6.6 (464)	27.0 ± 6.2 (448)	25.6[II] ± 6.7 (405)	26.2 ± 6.8 (389)	25.2 ± 6.8 (335)	25.0 ± 6.7 (334)	25.1 ± 6.8 (295)	23.2 ± 6.9 (193)	23.7 ± 6.9 (175)
Total rate ◊	26.7 ± 6.4 (488)	27.6[III] ± 6.6 (488)	27.5 ± 6.2 (479)	28.3 ± 6.3 (475)	27.1 ± 6.2 (456)	27.7 ± 6.7 (430)	27.0 ± 7.2 (423)	27.1 ± 7.1 (375)	27.0 ± 7.0 (383)	27.5 ± 7.0 (330)	26.5 ± 7.5 (263)	26.8 ± 7.2 (222)
Total MV †	11.3 ± 3.2 (469)	11.3 ± 3.7 (468)	10.4 ± 3.4 (469)	11.1[IV] ± 3.6 (467)	10.1 ± 2.7 (450)	10.9[V] ± 3.4 (423)	10.4 ± 3.1 (415)	10.9 ± 4.2 (362)	10.8 ± 3.4 (376)	10.8 ± 3.1 (318)	11.3 ± 3.6 (258)	11.0 ± 3.5 (217)
Set PEEP ‡	12.6 ± 3.6 (492)	12.5 ± 3.6 (495)	12.5 ± 4.4 (480)	13.4[VI] ± 4.2 (480)	10.8 ± 4.5 (456)	11.3 ± 4.5 (434)	10.3 ± 4.4 (424)	10.7 ± 4.6 (374)	9.7 ± 4.3 (384)	10.5[VII] ± 4.7 (332)	8.9 ± 4.2 (265)	9.6 ± 4.4 (223)
P_{IP} ‡	29.7 ± 8.5 (418)	30.4 ± 9.2 (427)	30.3 ± 6.8 (453)	31.1 ± 7.9 (425)	29.6 ± 7.4 (420)	29.9 ± 8.5 (377)	28.9 ± 7.7 (363)	28.5 ± 8.5 (303)	27.4 ± 7.8 (303)	28.5 ± 8.1 (262)	26.3 ± 8.5 (161)	28.0 ± 7.7 (149)
Plateau pressure ‡	25.5 ± 6.0 (274)	25.7 ± 6.1 (266)	25.2 ± 5.2 (382)	25.6 ± 5.6 (331)	24.3 ± 5.5 (348)	24.4 ± 6.3 (297)	23.6 ± 5.3 (282)	24.8[VIII] ± 6.0 (221)	23.3 ± 5.1 (223)	24.3 ± 6.1 (184)	22.3 ± 6.3 (103)	24.0 ± 5.7 (93)
Driving pressure ‡	12.7 ± 5.8 (274)	13.1 ± 5.9 (266)	12.8 ± 4.1 (382)	12.1[IX] ± 4.6 (331)	13.4 ± 4.2 (348)	12.6[X] ± 5.0 (297)	12.7 ± 4.6 (282)	13.4 ± 4.7 (221)	12.9 ± 4.7 (223)	12.8 ± 4.6 (184)	12.4 ± 5.9 (103)	13.2 ± 5.7 (93)
F_IO_2	0.80 ± 0.2 (489)	0.80 ± 0.2 (474)	0.49 ± 0.14 (436)	0.53[XI] ± 0.17 (408)	0.45 ± 0.13 (381)	0.49[XII] ± 0.16 (348)	0.47 ± 0.15 (331)	0.51[XIII] ± 0.17 (273)	0.47 ± 0.15 (291)	0.50 ± 0.16 (250)	0.48 ± 0.16 (188)	0.50 ± 0.17 (173)
pH	7.32 ± 0.10 (470)	7.32 ± 0.10 (474)	7.32 ± 0.10 (437)	7.33 ± 0.10 (409)	7.35 ± 0.08 (381)	7.36 ± 0.09 (348)	7.37 ± 0.08 (330)	7.37 ± 0.08 (277)	7.39 ± 0.08 (292)	7.39 ± 0.08 (252)	7.40 ± 0.10 (191)	7.41 ± 0.09 (178)
PaO_2 §	81.9 ± 24.7 (470)	82.4 ± 24.7 (474)	89.0 ± 30.7 (437)	92.0 ± 35.3 (409)	83.1 ± 27.2 (381)	86.5 ± 30.9 (348)	85.2 ± 26.9 (330)	85.4 ± 33.6 (277)	82.6 ± 27.8 (292)	82.7 ± 26.3 (251)	84.5 ± 30.4 (191)	86.5 ± 35.5 (178)
$PaCO_2$ §	44.1 ± 10.2 (470)	43.8 ± 12.0 (474)	46.5 ± 11.7 (437)	43.4[XIV] ± 10.6 (409)	45.6 ± 11.3 (381)	44.5 ± 12.3 (348)	45.0 ± 9.9 (330)	44.6 ± 11.4 (277)	43.9 ± 9.7 (292)	44.6 ± 10.4 (252)	43.7 ± 11.1 (191)	45.3 ± 11.7 (178)
PaO_2/F_IO_2 ^	116.1 ± 38.3 (469)	115.8 ± 40.1 (474)	198.4 ± 77.7 (436)	189.2 ± 76.8 (408)	198.0 ± 73.4 (381)	193.2 ± 79.0 (348)	197.8 ± 74.6 (330)	186.6 ± 75.6 (272)	190.6 ± 73.5 (289)	183.9 ± 80.0 (248)	197.5 ± 102.0 (188)	189.4± 80.6 (173)
OI "	17.2 ± 8.8 (425)	17.3 ± 10.0 (425)	10.8 ± 6.2 (420)	11.8[XV] ± 6.7 (382)	9.9 ± 5.9 (365)	10.8 ± 6.8 (328)	9.7 ± 6.3 (309)	10.9[XVI] ± 6.9 (247)	10.0 ± 7.1 (265)	11.2 ± 7.9 (222)	9.4 ± 7.2 (155)	10.0 ± 6.5 (135)

Plus-minus values are means ± SD with (no). PEEP denotes positive end-expiratory pressure, P_{IP} denotes peak inspiratory pressure, F_IO_2 denotes the fraction of inspired oxygen, PaO_2 denotes partial pressure of arterial oxygen, and $PaCO_2$ denotes the partial pressure of arterial carbon dioxide.

* measured in mL/kg, ◊ measured in breaths/min, † MV denotes minute ventilation measured in L/min, ‡ cmH_2O, § measured in mmHg, ^ measured in mmHg, " OI denotes oxygenation index, which equals F_IO_2 x mean airway pressure (cmH_2O) / PaO_2 (mmHg).

Differences with 95% CI: **I** 1.06 (0.24, 1.89), **II** 1.40 90.53, 2.26), **III** -0.83 (-1.65, -0.01), **IV** -0.66 (-1.11, -0.22), **V** -0.76, (-1.16, -0.35), **VI** -0.95 (-1.50, -0.41), **VII** -0.81 (-1.47, -0.15), **VIII** -1.25 (-2.25, -0.26), **IX** 0.68 (0.04, 1.31), **X** 0.78 (0.07, 1.49), **XI** -0.04 (-0.06, -0.02), **XII** -0.04 (-0.06, -0.02), **XIII** -0.03 (-0.05,0.00), **XIV** 3.14 (1.63, 4.64), **XV** -1.00 (-1.90, -0.11), **XVI** -1.19 (1.230, -0.09).

Table S6. Improvement in PaO_2/FIO_2 stratified by median duration of ARDS prior to randomization

		Proportion with PaO_2/FIO_2 ratio ≥300 mmHg			
		Day 1		Day 2	
Group	Median time	Intervention	Control	Intervention	Control
#1 (N=503)	3.7 hours	13% (27/210)	9% (20/222)	8% (15/182)	12% (22/185)
#2 (N=503)	15.6 hours	8% (17/226)	10% (18/186)	9% (17/199)	10% (16/163)
Difference (95% CI)		6% (-2% to 14%)		2% (-11% to 6%)	

Percentage (N/available records). PaO_2 denotes partial pressure of arterial oxygen, FIO_2 denotes the fraction of inspired oxygen. The groups were stratified by the median time for the entire cohort (7.6 hours) from first documentation of moderate-to-severe ARDS until randomization.

Table S7. Compliance with the study protocol high PEEP/FIO_2 table

Study day	Overall	Intervention	Control	Difference (95% CI)
Day 1	76.9% (738/960)	79.8% (383/480)	74.0% (355/480)	5.8% (0.5%, 11.2%)
Day 2	79.9% (711/890)	83.1% (379/456)	76.5% (332/434)	6.6% (1.3%, 11.9%)
Day 3	75.9% (606/798)	76.9% (326/424)	74.9% (280/374)	2.0% (-3.9%, 8.0%)
Day 4	73.7% (528/716)	71.9% (276/384)	75.9% (252/332)	-4.0% (-10.5%, 2.4%)
Day 7	64.5% (315/488)	63.4% (168/265)	65.9% (147/223)	-2.5% (-11.0%, 6.0%)

Percent (N/available records). PEEP denotes positive end-expiratory pressure, FIO_2 denotes the fraction of inspired oxygen. The full PEEP/FIO_2 table is on page 51 of the study protocol. Values represent combinations of FIO_2 and PEEP within 'in table' recommendations, as per study protocol, with specified exceptions to the PEEP table allowed for lower PEEP.

Table S8. Additional measures of 'on protocol' compliance

Measure	Overall	Intervention (N=501)	Control (N=505)	Difference (95% CI)
On target tidal volume * - % (No.)				
Day 1		88.2 (n=457)	86.7 (n=428)	1.5 (-2.9, 5.9)
Day 2		88.5 (n=425)	85.9 (n=377)	2.5 (-2.1, 7.2)
Day 3		88.0 (n=366)	83.5 (n=303)	4.5 (-0.9, 9.8)
Day 4		83.6 (n=304)	83.6 (n=262)	-0.0 (-6.2, 6.1)
Day 7		81.7 (n=164)	78.4 (n=148)	3.3 (-5.6, 12.2)
On target plateau pressure ◊ - % (No.)				
Day 1		87.4 (n=382)	83.4 (n=331)	4.1 (-1.2, 9.3)
Day 2		89.1 (n=348)	84.8 (n=297)	4.2 (-1.0, 9.5)
Day 3		91.5 (n=282)	86.4 (n=221)	5.1 (-0.5, 10.6)
Day 4		92.8 (n=223)	85.9 (n=184)	7.0 (0.9, 13.0)
Day 7		92.2 (n=113)	89.2 (n=93)	3.0 (-5.2, 11.1)
Fluid balance - mL (No.)				
Day 1	1136 [-109 - 2487] (n=964)	1310 [65-2716] (n=478)	956 [-208-2315] (n=486)	273 (-26, 572)
Day 2	327 [-951 - 1456] (n=918)	377 [-786 - 1532 (n=461)	304 [-1029 – 1383] (n=457)	116 (-153, 388)
Day 3	-242 [-1432 - 728] (n=889)	-355 [-1478 – 700] (n=452)	-169 [-1353 – 810] (n=537)	-81 (-368, 206)
Day 4	-455 [-1539 - 620] (n=858)	-576 [-1701 – 428] (n=438)	-214 [-1387 – 970] (n=420)	-369 (-623, -116)
Day 7	-301 [-1359 - 561] (n=7360	-330 [-1395 – 532] (n=375)	-274 [-1270 – 590] (n=361)	13 (-236., 262)
Cumulative fluid balance - mL (No.)				
Day 1	2712 [611 - 5206] (n=970)	2678 [835 - 5569] (n=482)	2795 [365-4866] (n=488)	360 (-219, 939)
Day 2	2984 [-110 - 6206] (n=924)	3133 [33 - 6691] (n=463)	2741 [-319 – 5759] (n=461)	445 (-270, 1161)
Day 3	2260 [-1289 - 6255] (n=897)	2533 [-1074 – 6892] (n=455)	2014 [-1406 – 5768] (n=442)	482 (-362, 1326)
Day 4	1795 [-2103 - 6182] (n=872)	1804 [-2132 – 5992] (n=442)	1751 [-2083 – 6629] (n=430)	7 (-847, 1006)
Day 7	198 [-4389 - 5261] (n=778)	168 [-4297 – 5017] (n=395)	231 [-4568 – 5790] (n=383)	-33 (-1173, 1106)

Reported as median and interquartile range, with number.

* Target tidal volume defined as <6.5 mL/kg ideal body weight.

◊ Target plateau pressure defined as <30 cmH_2O.

Table S9. Day 90 mortality percentage stratified by PaO_2/FIO_2 ratio

PaO_2/FIO_2 ratio	Intervention	Control	Difference (95% CI)	P-value
PaO_2/FIO_2 <120 mmHg (N=720)	42.5 ± 2.6 (362)	42.2 ± 2.6 (358)	0.4 (-6.9, 7.6)	
PaO_2/FIO_2 ≥120 mmHg (N=286)	42.4 ± 4.2 (139)	44.2 ± 4.1 (147)	-1.8 (-13.3, 9.7)	
Interaction			2.1 (-11.4, 15.7)	0.76

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

Table S10. Day 90 mortality percentage stratified by duration of ARDS prior to randomization

ARDS to randomization time	Intervention	Control	Difference (95% CI)	P-value
< median (N=503)	40.5 ± 3.2 (232)	44.6 ± 3.0 (271)	-4.1 (-12.8, 4.5)	
> median (N=503)	44.2 ± 3.0 (269)	40.6 ± 3.2 (234)	3.6 (-5.0, 12.3)	
Interaction			-7.8 (-20.0, 4.5)	0.21

Time measured from first documentation of moderate-to-severe ARDS until randomization. The overall median time was 7.6 hours. The median time for the cohort above the median was 15.6 hours, and that for those below the median was 3.7 hours. Mortality percentage - (# of patients who died/# of patients enrolled) x 100 ± StdErr (no.). P-value is calculated from Wald test.

Table s11. Day 90 mortality percentage stratified by hospital tercile for prior NMB use

Tercile	# hospitals; patients	Exclusion rate	Intervention	Control	Difference (95% CI)
#1	16; 443	9.2%	38.1 ± 3.3 (223)	40.0 ± 3.3 (220)	-1.9 (-11.0, 7.2)
#2	16; 375	25.7%	50.3 ± 3.7 (185)	45.8 ± 3.6 (190)	0.045 (-5.6, 14.6)
#3	16; 188	61.1%	37.6 ± 5.0 (93)	43.2 ± 5.1 (95)	-5.5 (-19.5, 8.5)
Interaction P-Value: 0.47					

NMB denotes neuromuscular blockade. Mortality percentage - (# of patients who died/# of patients enrolled) x 100 ± StdErr (no.). P-value is calculated from Wald test. Exclusion rate is the summed rate of patients excluded for prior NMB use/enrolled plus excluded for prior NMB use, weighted by sites' enrollment numbers.

Table S12. Day 90 mortality percentage estimates stratified by gender

Characteristic	Intervention	Control	Difference (95% CI)	P-value
Male (N=560)	42.6 ± 2.9 (291)	44.2 ± 3.0 (269)	-1.6 (-9.8, 6.6)	
Female (N=446)	42.4 ± 3.4 (210)	41.1 ± 3.2 (236)	1.3 (-7.9, 10.4)	
Interaction			-2.9 (-15.2, 9.4)	0.644

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

Table S13. Day 90 mortality percentage estimates stratified by race

Characteristic	Intervention	Control	Difference (95% CI)	P-value
Non-White (N=168)	47.4 ± 5.7 (76)	38.0 ± 5.1 (92)	9.3 (-5.7, 24.3)	
White (N=705)	41.6 ± 2.6 (361)	43.3 ± 2.7 (344)	-1.8 (-9.1, 5.5)	
Interaction			11.1 (-5.6, 27.8)	0.192

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

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.

Table S15. Day 90 mortality percentage stratified by hospital tercile for MD study refusal

Tercile	# hospitals; patients	Exclusion rate	Intervention	Control	Difference (95% CI)
#1	16; 279	1.4%	41.7 ± 4.2 (139)	42.1 ± 4.2 (140)	-0.4 (-12.0,11.2)
#2	16; 500	10.9%	42.0 ± 3.1 (250)	41.6 ± 3.1 (250)	0.4 (-8.2, 9.0)
#3	16; 227	45.2%	44.6 ± 4.7 (112)	46.1 ± 4.6 (115)	-1.4 (-14.4, 11.5)
Interaction P-Value: 0.97					

Mortality percentage - (# of patients who died/# of patients enrolled) x 100 ± StdErr (no.). P-value is calculated from Wald test. Exclusion rate is the summed rate of patients excluded for MD refusal/enrolled plus excluded for MD refusal, weighted by sites' enrollment numbers.

Table S16. Sequential Organ Failure Assessment (SOFA) scores

	SOFA score			Change in SOFA score from baseline		
	Intervention	Control	Difference (95% CI)	Intervention	Control	Difference (95% CI)
Coagulation						
Baseline	0.9 ± 1.2 (488)	0.9 ± 1.2 (496)	-	-	-	-
Day 1	1.0 ± 1.2 (468)	0.9 ± 1.2 (464)	0.1 (-0.1, 0.3)	0.1 ± 0.8 (468)	0.1 ± 0.8 (463)	0.0 (-0.1, 0.1)
Day 2	1.1 ± 1.3 (459)	1.0 ± 1.2 (442)	0.1 (-0.1, 0.2)	0.2 ± 0.9 (459)	0.2 ± 1.9 (441)	0.0 (-0.1, 0.1)
Day 3	1.0 ± 1.2 (434)	1.0 ± 1.2 (415)	0.0 (-0.1, 0.2)	0.1 ± 1.0 (434)	0.1 ± 1.0 (414)	0.0 (-0.1, 0.1)
Day 4	1.0 ± 1.2 (417)	1.0 ± 1.2 (387)	0.1 (-0.1, 0.2)	0.1 ± 1.1 (417)	0.11.0 (386)	0.0 (-0.1, 0.2)
Day 7	0.8 ± 1.2 (321)	0.7 ± 1.1 (297)	0.1 (-0.1, 0.3)	-0.1 ± 1.2 (321)	-0.2 ± 1.1 (296)	0.1 (-0.1, 0.3)
Liver						
Baseline	0.6 ± 1.1 (458)	0.6 ± 1.1 (467)	-	-	-	-
Day 1	0.6 ± 1.1 (440)	0.6 ± 1.1 (437)	0.0 (-0.1, 0.2)	0.1 ± 0.5 (440)	0.1 ± 0.6 (436)	0.0 (-0.1, 0.1)
Day 2	0.6 ± 1.1 (432)	0.6 ± 1.1 (415)	0.0 (-0.2, 0.1)	0.0 ± 0.5 (432)	0.1 ± 0.7 (414)	-0.1 (-0.2, 0.0)
Day 3	0.7 ± 1.2 (411)	0.7 ± 1.1 (391)	0.0 (-0.2, 0.1)	0.1 ± 0.7 (411)	0.1 ± 0.8 (390)	-0.1 (-0.2, 0.1)
Day 4	0.7 ± 1.2 (395)	0.7 ± 1.1 (366)	0.0 (-0.2, 0.2)	0.1 ± 0.8 (395)	0.2 ± 0.8 (365)	0.0 (-0.2, 0.1)
Day 7	0.7 ± 1.2 (305)	0.7 ± 1.2 (282)	0.1 (-0.3, 0.1)	0.1 ± 0.8 (305)	0.2 ± 1.0 (281)	-0.1 (-0.3, 0.0)
Cardiovascular						
Baseline	2.3 ± 1.6 (488)	2.5 ± 1.6 (496)	-	-	-	-
Day 1	2.8 ± 1.5 (468)	2.5 ± 1.5 (464)	0.2 (0.1, 0.4)	0.5 ± 1.5 (468)	0.1 ± 1.3 (463)	0.4 (0.2, 0.6)
Day 2	2.4 ± 1.5 (458)	2.1 ± 1.6 (442)	0.3 (0.1, 0.5)	0.2 ± 1.6 (458)	-0.3 ± 1.6 (441)	0.5 (0.3, 0.7)
Day 3	2.0 ± 1.5 (434)	1.8 ± 1.5 (415)	0.2 (0.0, 0.4)	-0.2 ± 1.8 (434)	-0.6 ± 1.7 (414)	0.3 (0.1, 0.6)
Day 4	1.6 ± 1.5 (417)	1.5 ± 1.5 (386)	0.1 (-0.1, 0.3)	-0.6 ± 1.8 (417)	-0.9 ± 1.7 (385)	0.3 (0.0, 0.5)
Day 7	1.1 ± 1.3 (321)	1.4 ± 1.4 (297)	-0.2 (-0.4, 0.0)	-1.1 ± 1.8 (321)	-1.1 ± 1.8 (296)	0.0 (-0.2, 0.3)
Renal						
Baseline	1.6 ± 1.5 (488)	1.6 ± 1.6 (496)	-	-	-	-
Day 1	1.6 ± 1.6 (468)	1.6 ± 1.6 (464)	0.0 (-0.2, 0.2)	0.0 ± 1.1 (468)	0.1 ± 1.1 (463)	0.0 (-0.2, 0.1)
Day 2	1.6 ± 1.6 (459)	1.6 ± 1.6 (442)	0.0 (-0.2, 0.3)	0.0 ± 1.2 (459)	0.1 ± 1.2 (441)	0.0 (-0.2, 0.2)
Day 3	1.7 ± 1.6 (434)	1.6 ± 1.7 (415)	0.1 (-0.1, 0.3)	0.1 ± 1.3 (434)	0.1 ± 1.2 (414)	0.1 (-0.1, 0.2)
Day 4	1.6 ± 1.7 (417)	1.6 ± 1.7 (387)	0.0 (-0.2, 0.2)	0.0 ± 1.4 (417)	0.1 ± 1.4 (386)	0.0 (-0.2, 0.2)
Day 7	1.6 ± 1.6 (321)	1.7 ± 1.7 (297)	-0.1 (-0.3, 0.2)	0.0 ± 1.5 (321)	0.1 ± 1.5 (296)	0.0 (-0.3, 0.2)
Non-pulmonary SOFA Total Score (excluding neurologic)						
Baseline	5.5 ± 3.4 (488)	5.6 ± 3.4 (496)	-	-	-	-
Day 1	6.0 ± 3.7 (468)	5.7 ± 3.6 (464)	0.4 (-0.1, 0.8)	0.7 ± 2.0 (468)	0.3 ± 2.0 (463)	0.4 (0.2, 0.7)
Day 2	5.7 ± 3.9 (459)	5.3 ± 3.7 (442)	0.4 (-0.1, 0.9)	0.4 ± 2.3 (459)	0.0 ± 2.5 (441)	0.4 (0.1, 0.7)
Day 3	5.3 ± 4.0 (434)	5.0 ± 3.7 (415)	0.3 (-0.2, 0.8)	0.1 ± 2.6 (434)	-0.3 ± 2.7 (414)	0.3 (0.0, 0.7)
Day 4	4.8 ± 4.2 (417)	4.6 ± 3.7 (387)	0.2 (-0.4, 0.7)	-0.4 ± 2.8 (417)	-0.6 ± 2.8 (386)	0.2 (-0.2, 0.6)
Day 7	4.2 ± 3.7 (321)	4.4 ± 3.8 (297)	-0.3 (-0.9, 0.3)	-1.1 ± 3.0 (321)	-1.0 ± 3.2 (296)	0.0 (-0.5, 0.5)

Plus-minus values are means ± SD (no.). Individual organ SOFA scores: range from 0 to 4, with higher scores indicative of worse organ dysfunction.[11] Coagulation is based on platelet count, liver on total bilirubin, cardiovascular on mean arterial pressure and vasopressor utilization, and renal on creatinine and urine output. Total SOFA score is the sum of individual organ scores.

Table S17. Organ failure free days

Organ failure free days by day 28	Intervention (N=501)	Control (N=505)	Difference (95% CI)
Any organ	12.4 ± 11.3 (n=480)	12.5 ± 11.5 (n=479)	-0.1 (-1.5, 1.4)
Cardiovascular	16.8 ± 11.4 (n=493)	16.6 ± 11.7 (n=497)	0.2 (-1.3, 1.6)
Coagulation	17.5 ± 11.8 (n=499)	17.7 ± 11.8 (n=504)	-0.2 (-1.7, 1.2)
Hepatic	17.9 ± 11.9 (n=471)	17.4 ± 11.9 (n=477)	0.6 (-1.0, 2.1)
Renal	15.3 ± 11.8 (n=499)	15.4 ± 11.9 (n=504)	-0.1 (-1.6, 1.4)

Plus-minus values are means ± SD with (no.). We calculated the number of days without organ failure by subtracting the number of days with organ failure from the lesser of 28 days or the number of days to death if death occurred prior to day 29. Organs and systems were considered failure-free after patients were discharged from the hospital. For each organ, failure was defined as a sequential organ failure assessment (SOFA) score >2 (range: 0-4, where higher scores = greater dysfunction). No neurologic score was collected or assessed.[11]

Table S18. Use of adjunctive therapies

	Day 0-2			Day 0-28		
Characteristic	Intervention	Control	Difference (95% CI)	Intervention	Control	Difference (95% CI)
Any rescue therapy	93 (18.6)	90 (17.8)	0.7 (-4.0, 5.5)	130 (25.9)	125 (24.8)	1.2 (-4.2, 6.6)
Prone positioning	68 (13.6)	60 (11.9)	1.7 (-2.4, 5.8)	84 (16.8)	75 (14.9)	1.9 (-2.6, 6.4)
Inhaled epoprostenol	16 (3.2)	17 (3.4)	-0.2 (-2.4, 2.0)	26 (5.2)	27 (5.3)	-0.2 (-2.9, 2.6)
Recruitment maneuvers	14 (2.8)	16 (3.2)	-0.4 (-2.5, 1.7)	29 (5.8)	30 (5.9)	-0.2 (-3.1, 2.8)
Inhaled nitric oxide	4 (0.8)	12 (2.4)	-1.6 (-3.1, 0.0)	7 (1.4)	17 (3.4)	-2.0 (-3.8, -0.1)
ECMO	2 (0.4)	3 (0.6)	-0.2 (-1.1, 0.7)	3 (0.6)	10 (2.0)	-1.4 (-2.8, 0.0)

No. (%). Denominators are 501 and 505 in the intervention and control groups. ECMO denotes extracorporeal membrane oxygenation.

Table S19. Glucocorticoid use during the first week

Study day	Overall	Intervention	Control	Difference (95% CI)
Day 1	25.2% (244/970)	22.6% (109/482)	27.7% (135/488)	-5.0% (-10.5%, 0.4%)
Day 2	24.2% (224/924)	22.7% (105/463)	25.8% (119/461)	-3.1% (-8.7%, 2.4%)
Day 3	23.1% (207/897)	22.2% (101/455)	24.0% (106/442)	-1.8% (-7.3%, 3.7%)
Day 4	21.1% (184/872)	20.6% (91/442)	21.6% (93/430)	-1.0% (-6.5%, 4.4%)
Day 7	16.7% (130/778)	17.0% (67/395)	16.4% (63/383)	0.5% (-4.7%, 5.8%)

Percentage determined by N / available records.

Table S20. All-location mortality percentage estimates at study day 90 and day 365

Study day	Intervention	Control	Difference (95% CI)	P-value
Day 90	45.3 ± 2.2	45.3 ± 2.2	0.0 ± 3.1	0.99
Day 365	51.1 ± 2.2	51.1 ± 2.2	0.0 ± 3.2	0.98

The mortality percentages are the point estimates for days 90 and 365 taken from the non-parametric interval censored survival functions (see Statistical Analysis in the Methods section of the paper). P-value is calculated from a Z test.

Table S21. Outcomes at 3 months

Characteristic	Intervention	Control	Difference (95% CI)
Assessments			
EQ-5D-5L *	0.66 ± 0.41 (n=207)	0.73 ± 0.39 (n=194)	0.0 (-0.1, 0.1)
Difficulty in a daily activity - no./available records (%) ◊	168/212 (79.2)	154/196 (78.6)	0.7 (-7.3, 8.6)
Disability Score †	3.3 ± 2.7 (n=212)	3.0 ± 2.7 (n=196)	0.3 (-0.3, 0.8)
Self-rated Health ‡	3.4 ± 1.1 (n=164)	3.3 ± 1.0 (n=158)	0.1 (-0.1, 0.3)
Pain Interference §	2.6 ± 1.4 (n=162)	2.6 ± 1.4 (n=157)	0.0 (-0.3, 0.3)
PTSS - no. (%) ^	-	-	
MoCA blind "	22.2 ± 5.2 (n=154)	22.8 ± 4.8 (n=133)	-0.6 (-1.7, 0.6)
AD8 scores #	3.1 ± 2.8 (n=45)	2.5 ± 2.6 (n=37)	0.6 (-0.6, 1.8)
Other outcomes - no./available records (%)			
Location of residence % home	173/212 (81.6)	161/195 (82.6)	-1.0 (-8.4, 6.5)
Hospital readmission	69/211 (32.7)	63/195 (32.3)	0.4 (-8.7, 9.5)
ER visit	46/211 (21.8)	32/195 (16.4)	5.4 (-2.2, 13.0)
Return to work - no./available records (%)	32/212 (15.1)	34/196 (17.3)	-2.3 (-9.4, 4.9)
Significant change in work duties	77/119 (64.7)	68/107 (63.6)	1.2 (-11.4, 13.7)
Impact on daily activities - no. (%)	(n=246)	(n=238)	
Eating	45 (18.3)	36 (15.1)	3.2 (-3.5, 9.8)
Getting in or out of bed	93 (37.8)	84 (35.3)	2.5 (-6.1, 11.1)
Using the toilet	82 (33.3)	66 (27.7)	5.6 (-2.6, 13.8)
Preparing a hot meal	67 (27.2)	66 (27.7)	-0.5 (-8.5, 7.5)
Making phone calls	43 (17.5)	37 (15.5)	1.9 (-4.7, 8.5)
Taking medications	49 (19.9)	44 (18.5)	1.4 (-5.6, 8.4)
Managing money	40 (16.3)	46 (19.3)	-3.1 (-9.9, 3.7)
Shopping for groceries	97 (39.4)	87 (36.6)	2.9 (-5.8, 11.5)
Stooping, kneeling or crouching	154 (62.6)	158 (66.4)	-3.8 (-12.3, 4.7)
Lifting/carrying weights >10 pounds	145 (58.9)	139 (58.4)	

Plus-minus values are means ± SD.

* The EQ-5D-5L ranges from -0.109 to 1; higher scores indicate better quality of life, with less than 0 a state assessed by general population norms to be worse than death and 1 indicating good health.[5]

◊ Difficulty in a daily activity is the percentage reporting any difficulty in any of the 10 Katz Activity of Daily Living (ADL), Lawton Instrumental Activities of Daily Living (IADL), or Nagi scale items asked.[6]

† The Disability score ranges from 0 to 10 and is the number of those 10 ADL/IADL/Nagi items on which the respondent or their proxy reported difficulty due to health conditions, with higher scores representing worse disability, and scores of 4 or greater interpretable as representing severe disability.[6]

‡ Self-rated health was a five-point categorical score with 1 indicating excellent health and 5 indicating poor health.

§ Pain interference was a five-point categorical score with 1 indicating no interference with one's daily life and 5 indicating extreme interference.

^ The PTSS-14 ranges from 14 to 98, with higher scores indicate more symptoms, and with scores above 45 indicating a threshold for a higher likelihood of post-traumatic stress-like symptoms.[7]

" MOCA Blind score measures cognition where the individual themselves can be tested, ranging up to 30; scores above 26 are considered the normal range for cognition.[8]

AD8 scores are used to assess cognition by proxies for the subset of patients alive but not able to respond themselves; AD8 scores range 0 to 8, with high scores suggesting worse cognitive function and scores greater than 2 indicating that cognitive impairment is likely to be present.[9]

Table S22. Outcomes at 6 months

Characteristic	Intervention	Control	Difference (95% CI)
Assessments			
EQ-5D-5L *	0.74 ± 0.27 (n=176)	0.79 ± 0.28 (n=155)	0.0 (-0.1, 0.1)
Difficulty in a daily activity - no./available records (%) ◊	140/180 (77.8)	126/156 (80.8)	-3.0 (-11.7, 5.7)
Disability Score †	2.7 ± 2.4 (n=180)	2.7 ± 2.4 (n=156)	0.1 (-0.5, 0.6)
Self-rated Health ‡	3.2 ± 1.0 (n=149)	3.3 ± 1.0 (n=132)	-0.1 (-0.3, 0.2)
Pain Interference §	2.6 ± 1.3 (n=148)	2.4 ± 1.2 (n=132)	0.2 (-0.1, 0.5)
PTSS - no. (%) ^	38/145 (26.2)	31/122 (25.4)	0.8 (-9.7, 11.3)
MoCA blind "	22.8 ± 4.8 (n=138)	23.2 ± 5.1 (n=114)	-0.3 (-1.6, 0.9)
AD8 scores #	2.2 ± 2.8 (n=31)	3.3 ± 2.7 (n=24)	-1.1 (-2.6, 0.4)
Other outcomes - no./available records (%)			
Location of residence % home	164/180 (91.1)	147/156 (94.2)	-3.1 (-8.7, 2.4)
Hospital readmission	46/180 (25.6)	43/156 (27.6)	-2.0 (-11.5, 7.5)
ER visit	38/180 (21.1)	31/156 (19.9)	1.2 (-7.4, 9.9)
Return to work - no./available records (%)	40/180 (22.2)	31/156 (19.9)	2.4 (-6.4, 11.1)
Significant change in work duties	37/85 (43.5)	34/73 (46.6)	-3.0 (-18.6, 12.5)
Impact on daily activities – no. (%)	(n=218)	(n=192)	
Eating	32 (14.7)	20 (10.4)	4.3 (-2.1, 10.7)
Getting in or out of bed	63 (29.0) (n=217)	40 (20.8)	8.2 (-0.1, 16.5)
Using the toilet	49 (22.6) (n=217)	41 (21.4)	1.2 (-6.8, 9.3)
Preparing a hot meal	48 (22.1) (n=217)	40 (20.8)	1.3 (-6.7, 9.3)
Making phone calls	27 (12.4)	20 (10.4)	2.0 (-4.1, 8.2)
Taking medications	27 (12.4)	25 (13.0)	-0.6 (-7.1, 5.9)
Managing money	43 (19.8) (n=217)	35 (18.2)	1.6 (-6.0, 9.2)
Shopping for groceries	75 (34.6) (n=217)	64 (33.3)	1.2 (-8.0, 10.4)
Stooping, kneeling or crouching	134 (61.8) (n=217)	126 (65.6)	-3.9 (-13.2, 5.5)
Lifting/carrying weights >10 pounds	114 (52.5) (n=217)	106 (55.2)	-2.7 (-12.3, 7.0)

Plus-minus values are means ± SD.

* The EQ-5D-5L ranges from -0.109 to 1; higher scores indicate better quality of life, with less than 0 a state assessed by general population norms to be worse than death and 1 indicating good health.[5]

◊ Difficulty in a daily activity is the percentage reporting any difficulty in any of the 10 Katz Activity of Daily Living (ADL), Lawton Instrumental Activities of Daily Living (IADL), or Nagi scale items asked.[6]

† The Disability score ranges from 0 to 10 and is the number of those 10 ADL/IADL/Nagi items on which the respondent or their proxy reported difficulty due to health conditions, with higher scores representing worse disability, and scores of 4 or greater interpretable as representing severe disability.[6]

‡ Self-rated health was a five-point categorical score with 1 indicating excellent health and 5 indicating poor health.

§ Pain interference was a five-point categorical score with 1 indicating no interference with one's daily life and 5 indicating extreme interference.

^ The PTSS-14 ranges from 14 to 98, with higher scores indicate more symptoms, and with scores above 45 indicating a threshold for a higher likelihood of post-traumatic stress-like symptoms.[7]

" MOCA Blind score measures cognition where the individual themselves can be tested, ranging up to 30; scores above 26 are considered the normal range for cognition.[8]

AD8 scores are used to assess cognition by proxies for the subset of patients alive but not able to respond themselves; AD8 scores range 0 to 8, with high scores suggesting worse cognitive function and scores greater than 2 indicating that cognitive impairment is likely to be present.[9]

Table S23. Outcomes at 12 months

Characteristic	Intervention	Control	Difference (95% CI)
Assessments			
EQ-5D-5L *	0.75 ± 0.26 (n=127)	0.77 ± 0.29 (n=119)	0.0 (-0.1, 0.1)
Difficulty in a daily activity - no./available records (%) ◊	100/128 (78.1)	89/119 (74.8)	3.3 (-7.3, 13.9)
Disability Score †	2.9 ± 2.6 (n=128)	2.4 ± 2.3 (n=119)	0.5 (-0.1, 1.1)
Self-rated Health ‡	3.3 ± 1.0 (n=107)	3.3 ± 1.0 (n=100)	0.0 (-0.3, 0.3)
Pain Interference §	2.4 ± 1.3 (n=107)	2.5 ± 1.3 (n=99)	-0.1 (-0.4, 0.3)
PTSS - no. (%) ^	21/103 (20.4)	38/94 (40.4)	-20.0 (-32.6, -7.4)
MoCA blind "	23.3 ± 4.9 (n=99)	24.0 ± 4.4 (n=88)	-0.8 (-2.1, 0.6)
AD8 scores #	3.6 ± 3.1 (n=22)	2.8 ± 2.8 (n=19)	0.8 (-1.1, 2.7)
Other outcomes - no./available records (%)			
Location of residence % home	121/128 (94.5)	113/119 (95.0)	-0.4 (-6.0, 5.1)
Hospital readmission	47/128 (36.7)	43/118 (36.4)	0.3 (-11.8, 12.3)
ER visit	38/127 (29.9)	31/118 (26.3)	3.7 (-7.6, 14.9)
Return to work - no./available records (%)	25/127 (19.7)	26/119 (21.8)	-2.2 (-12.3, 8.0)
Significant change in work duties	19/43 (44.2)	22/54 (40.7)	3.4 (-16.4, 23.2)
Impact on daily activities - no. (%)	(n=163)	(n=153)	
Eating	24 (14.7)	16 (10.5) (n=152)	4.3 (-3.0, 11.6)
Getting in or out of bed	44 (27.0)	37 (24.2)	2.8 (-6.8, 12.4)
Using the toilet	33 (20.2)	37 (24.2)	-3.9 (-13.1, 5.2)
Preparing a hot meal	30 (18.4)	34 (22.2)	-3.8 (-12.7, 5.1)
Making phone calls	21 (12.9)	21 (13.7)	-0.8 (-8.3, 6.7)
Taking medications	28 (17.2)	26 (17.0)	0.2 (-8.1, 8.5)
Managing money	38 (23.3)	26 (17.0)	6.3 (-2.5, 15.1)
Shopping for groceries	59 (36.2)	48 (31.4)	4.8 (-5.6, 15.2)
Stooping, kneeling or crouching	107 (65.6)	96 (62.7)	2.9 (-7.7, 13.5)
Lifting/carrying weights 10 pounds	85 (52.1)	77 (50.3)	1.8 (-9.2, 12.8)

Plus-minus values are means ± SD.

* The EQ-5D-5L ranges from -0.109 to 1; higher scores indicate better quality of life, with less than 0 a state assessed by general population norms to be worse than death and 1 indicating good health.[5]

◊ Difficulty in a daily activity is the percentage reporting any difficulty in any of the 10 Katz Activity of Daily Living (ADL), Lawton Instrumental Activities of Daily Living (IADL), or Nagi scale items asked.[6]

† The Disability score ranges from 0 to 10 and is the number of those 10 ADL/IADL/Nagi items on which the respondent or their proxy reported difficulty due to health conditions, with higher scores representing worse disability, and scores of 4 or greater interpretable as representing severe disability.[6]

‡ Self-rated health was a five-point categorical score with 1 indicating excellent health and 5 indicating poor health.

§ Pain interference was a five-point categorical score with 1 indicating no interference with one's daily life and 5 indicating extreme interference.

^ The PTSS-14 ranges from 14 to 98, with higher scores indicate more symptoms, and with scores above 45 indicating a threshold for a higher likelihood of post-traumatic stress-like symptoms.[7]

" MOCA Blind score measures cognition where the individual themselves can be tested, ranging up to 30; scores above 26 are considered the normal range for cognition.[8]

AD8 scores are used to assess cognition by proxies for the subset of patients alive but not able to respond themselves; AD8 scores range 0 to 8, with high scores suggesting worse cognitive function and scores greater than 2 indicating that cognitive impairment is likely to be present.[9]

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.

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
Gastrointestinal	Ileus	Non-Serious	0	1	1	0.32
General	Death *	Serious	1	0	1	0.32
Infection	Pneumonia	Non-Serious	0	1	1	0.32
Injury	Paralysis awareness	Non-Serious	1	0	1	0.32
Metabolism/nutrition	Hyperkalemia	Serious	0	1	1	0.32
Musculoskeletal	Myopathy	Non-Serious	1	0	1	0.32
Nervous system	Intracranial bleed	Serious	0	1	1	0.32
	Cerebral infarction	Serious	1	1	2	1.0
	Cerebrovascular accident	Serious	1	0	1	0.32
	Brain hemorrhage	Serious	1	1	2	1.0
	Polyneuropathy	Serious	0	1	1	0.32
	Seizure	Serious	1	0	1	0.32
	Stroke	Serious	3	1	4	0.32
	Subarachnoid hemorrhage	Serious	0	1	1	0.32
	Subdural effusion	Serious	1	0	1	0.32

System/disorder	Event	Severity	Intervention	Control	Overall	P-value
Respiratory tract	Aspiration	Serious	0	1	1	0.18
		Non-Serious	0	1	1	
	Airway obstruction	Serious	1	0	1	0.32
Vascular disorders	Hematoma	Serious	0	1	1	0.32
	Retroperitoneal hemorrhage	Non-Serious	0	1	1	0.32
	Hypotension	Serious	1	1	2	0.32
		Non-Serious	6	2	8	
	Superficial venous thrombosis	Non-Serious	1	0	1	0.32

Adverse events were compared between groups with the event the unit of analysis. P-value calculated from weighted Poisson regression with non-serious events weighted by one and serious events weighted by two.

* Although mortality was high in both groups, only one death was considered 'possibly related' to study drug.

Table S26. Mortality percentage estimates during the first 48 and 96 hours

Time	Intervention (N=501)	Control (N=505)	Difference (95% CI)	P-value
First 48 hours	8.4 (n=42)	11.1 (n=56)	-2.7 (-6.4 to 1.0)	0.15
First 96 hours	12.5 (n=63)	15.8 (n=80)	-3.3 (-7.6 to 1.0)	0.14

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

Table S27. In-hospital recall assessments

Characteristic	Intervention (N=181)	Control (N=198)	Difference (95% CI)
Remember something - no. (%)	47 (26.0)	56 (28.3)	-2.3 (-11.3, 6.6)
First thing you remember after waking up - no. (%)			
Other	49 (27.1)	50 (25.3)	-
Being in the ICU	29 (16.0)	19 (9.6)	-
Nothing	26 (14.4)	28 (14.1)	-
Hearing voices	24 (13.3)	19 (9.6)	-
Being with family	23 (12.7)	33 (16.7)	-
Feeling breathing tube	22 (12.2)	33 (16.7)	-
Feeling pain	6 (3.3)	14 (7.1)	-
Feeling mask on face	2 (1.1)	2 (1.0)	-
Dreamed in ICU - no. (%)	73 (40.3)	84 (42.4)	-2.1 (-12.0, 7.8)
Disturbing ICU dream - no. (%) *	41 (56.2)	49 (58.3)	-2.2 (-17.7, 13.3)
Worse thing in ICU - no. (%)			
Other	75 (41.4)	87 (43.9)	-
Unable to carry out usual activities	53 (29.3)	39 (19.7)	-
Anxiety	17 (9.4)	30 (15.2)	-
Pain	15 (8.3)	17 (8.6)	-
Recovery process	12 (6.6)	18 (9.1)	-
Awareness	9 (5.0)	7 (3.5)	-

* Intervention (n=73), control (n=84). ICU denotes intensive care unit.

Table S28. In-hospital neuromuscular assessments

Characteristic	Intervention (N=501)	Control (N=505)	Difference (95% CI)
Moved arms or legs on day 3 - no. (%)	(n=455)	(n=442)	-9.9 (-16.4, -3.4)
No	257 (56.5)	206 (46.6)	
Yes	198 (43.5)	236 (53.4)	
Highest level of physical activity - no. (%) *◊			
Day 1	(n=482)	(n=488)	
None	470 (97.5)	438 (89.8)	-7.8% (-10.8%, -4.7%) ◊
Sitting/exercising in bed	11 (2.3)	37 (7.6)	
Passively moving to chair	1 (0.2)	0 (0.0)	
Sitting over edge of bed or more	0 (0.0)	2 (0.4)	
Day 2	(n=463)	(n=461)	
None	436 (94.2)	376 (81.6)	-12.6% (-16.7%, -8.5%) ◊
Sitting/exercising in bed	17 (3.7)	49 (10.6)	
Passively moving to chair	4 (0.9)	5 (1.1)	
Sitting over edge of bed or more	6 (1.2)	31 (6.7)	
Day 3	(n=455)	(n=442)	
None	384 (84.4)	332 (75.1)	-9.3% (-14.5%, -4.1%) ◊
Sitting/exercising in bed	42 (9.2)	66 (14.9)	
Passively moving to chair	7 (1.5)	6 (1.4)	
Sitting over edge of bed or more	4 (0.9)	6 (1.4)	
Day 4	(n=442)	(n=430)	
None	345 (78.1)	299 (69.5)	-8.5% (-14.3%, -2.7%) ◊
Sitting/exercising in bed	51 (11.5)	59 (13.7)	
Passively moving to chair	9 (2.0)	6 (1.4)	
Sitting over edge of bed or more	2 (0.5)	12 (2.8)	
Day 5	(n=431)	(n=414)	
None	313 (72.6)	271 (65.5)	-7.2% (-13.4%, -0.9%) ◊
Sitting/exercising in bed	58 (13.5)	60 (14.5)	
Passively moving to chair	8 (1.9)	12 (2.9)	
Sitting over edge of bed or more	5 (1.2)	8 (1.9)	
Day 6	(n=412)	(n=397)	
None	280 (68.0)	238 (59.9)	-8.0% (-14.6%, -1.4%) ◊
Sitting/exercising in bed	50 (12.1)	63 (15.9)	
Passively moving to chair	16 (3.9)	13 (3.3)	
Sitting over edge of bed or more	6 (1.5)	9 (2.3)	
Day 7	(n=395)	(n=383)	
None	244 (61.8)	212 (55.4)	-6.4% (-13.3%, 0.5%) ◊
Sitting/exercising in bed	49 (12.4)	60 (15.7)	
Passively moving to chair	24 (6.1)	12 (3.1)	
Sitting over edge of bed or more	14 (3.5)	9 (2.3)	

Characteristic	Intervention (N=501)	Control (N=505)	Difference (95% CI)
Manual muscle testing – means ± SD, (no.) †			
Right Shoulder Abduction			
Day 7	3.8 ± 1.3 (121)	4.1 ± 1.1 (131)	-0.3 (-0.6, 0.0)
Day 14	4.0 ± 1.1 (110)	3.9 ± 1.2 (116)	0.0 (-0.3, 0.4)
Day 21	3.8 ± 1.4 (73)	4.0 ± 1.1 (84)	-0.2 (-0.6, 0.3)
Day 28	3.6 ± 1.5 (50)	4.1 ± 1.0 (53)	-0.5(-1.0, 0.0)
Left Shoulder Abduction			
Day 7	3.8 ± 1.4 (124)	4.1 ± 1.2 (132)	-0.3 (-0.6, 0.0)
Day 14	4.0 ± 1.2 (109)	3.9 ± 1.2 (114)	0.0 (-0.3, 0.3)
Day 21	3.8 ± 1.4 (72)	3.9 ± 1.2 (82)	-0.1 (-0.6, 0.3)
Day 28	3.6 ± 1.4 (50)	4.0 ± 1.0 (52)	-0.5 (-1,0, 0.0)
Right Elbow Flexion			
Day 7	4.0 ± 1.2 (126)	4.2 ± 1.1 (132)	-0.2 (-0.5, 0.1)
Day 14	4.1 ± 1.0 (111)	4.1 ± 1.2 (117)	0.0 (-0.3, 0.3)
Day 21	3.9 ± 1.4 (75)	4.1 ± 1.0 (84)	-0.2 (-0.6, 0.2)
Day 28	4.0 ± 1.2 (48)	4.3 ± 0.9 (54)	-0.2 (-0.7, 0.2)
Left Elbow Flexion			
Day 7	4.0 ± 1.2 (126)	4.1 ± 1.1 (131)	-0.1 (-0.4, 0.2)
Day 14	4.1 ± 1.1 (110)	4.1 ± 1.1 (117)	0.0 (-0.3, 0.3)
Day 21	3.9 ± 1.4 (75)	4.1 ± 1.1 (82)	-0.2 (-0.6, 0.2)
Day 28	4.0 ± 1.1 (48)	4.2 ± 0.9 (54)	-0.2 (-0.6, 0.2)
Right Wrist Extension			
Day 7	4.0 ± 1.2 (126)	4.3 ± 1.1 (129)	-0.2 (-0.5, 0.1)
Day 14	4.2 ± 1.0 (109)	4.2 ± 1.1 (118)	0.1 (-0.2, 0.3)
Day 21	3.9 ± 1.4 (74)	4.2 ± 1.0 (83)	-0.3 (-0.7, 0.1)
Day 28	4.0 ± 1.2 (46)	4.4 ± 0.9 (54)	-0.4 (-0.8, 0.0)
Left Wrist Extension			
Day 7	4.1 ± 1.2 (125)	4.2 ± 1.1 (130)	-0.2 (-0.4, 0.1)
Day 14	4.2 ± 1.1 (108)	4.2 ± 1.0 (117)	0.0 (-0.3, 0.3)
Day 21	3.8 ± 1.4 (74)	4.1 ± 1.1 (81)	-0.3 (-0.7, 0.1)
Day 28	4.0 ± 1.2 (47)	4.3 ± 0.9 (53)	-0.3 (-0.7, 0.1)
Right Hip Flexion			
Day 7	3.7 ± 1.5 (118)	3.9 ± 1.3 (125)	-0.3 (-0.6, 0.1)
Day 14	3.8 ± 1.2 (99)	3.7 ± 1.3 (108)	0.1 (-0.2, 0.5)
Day 21	3.7 ± 1.5 (69)	3.6 ± 1.3 (77)	0.1 (-0.4, 0.5)
Day 28	3.6 ± 1.5 (43)	3.8 ± 1.3 (49)	-0.3 (-0.5, 0.3)
Left Hip Flexion			
Day 7	3.7 ± 1.4 (113)	3.9 ± 1.3 (123)	-0.2 (-0.5, 0.2)
Day 14	3.8 ± 1.2 (96)	3.8 ± 1.2 (109)	0.0 (-0.3, 0.4)
Day 21	3.7 ± 1.5 (68)	3.5 ± 1.4 (75)	0.2 (-.3, 0.3)
Day 28	3.6 ± 1.4 (42)	3.7 ± 1.3 (48)	-0.1 (-0.7, 0.5)
Right Knee Extension			
Day 7	3.8 ± 1.4 (119)	4.1 ± 1.2 (128)	-0.3 (-0.6, 0.1)
Day 14	4.0 ± 1.1 (101)	3.9 ± 1.3 (114)	0.0 (-0.3, 0.3)
Day 21	3.7 ± 1.5 (72)	3.9 ± 1.3 (79)	-0.2 (-0.6, 0.3)
Day 28	3.8 ± 1.4 (47)	4.0 ± 1.2 (50)	-0.2 (-0.8, 0.3)

Characteristic	Intervention (N=501)	Control (N=505)	Difference (95% CI)
Left Knee Extension			
Day 7	3.9 ± 1.3 (114)	4.1 ± 1.2 (128)	-0.2 (-0.5, 0.1)
Day 14	4.0 ± 1.1 (96)	4.0 ± 1.2 (113)	-0.1 (-0.4, 0.2)
Day 21	3.7 ± 1.4 (70)	3.8 ± 1.3 (76)	-0.2 (-0.6, 0.3)
Day 28	3.8 ± 1.3 (44)	4.0 ± 1.2 (49)	-0.2 (-0.7, 0.3)
Right Foot Dorsiflexion			
Day 7	4.0 ± 1.3 (118)	4.2 ± 1.2 (130)	-0.1 (-0.5, 0.2)
Day 14	4.1 ± 1.1 (104)	4.2 ± 1.1 (117)	0.0 (-0.3, 0.3)
Day 21	3.9 ± 1.4 (72)	4.3 ± 0.9 (79)	-0.4 (-0.8, 0.0)
Day 28	3.7 ± 1.4 (46)	4.3 ± 1.0 (51)	-0.6 (-1.1, -0.1)
Left Foot Dorsiflexion			
Day 7	4.0 ± 1.3 (113)	4.2 ± 1.2 (127)	-0.2 (-0.5, 0.2)
Day 14	4.1 ± 1.0 (97)	4.2 ± 1.1 (116)	0.0 (-0.3, 0.3)
Day 21	3.8 ± 1.4 (70)	4.2 ± 1.0 (75)	-0.4 (-0.8, 0.0)
Day 28	3.7 ± 1.4 (42)	4.3 ± 0.9 (52)	-0.6 (-1.1, 0.2)

Plus-minus values are means ± SD with (no.).

* Physical activity was assessed with a condensed ICU mobility scale.[12] Normal range 0-10, where 0 = not actively moving, 1 sitting and exercising in bed, 2 passively moving to a chair, or 3 or move sitting over edge of bed to walking independently without a gait aid.

◊ Highest level of daily activity was analyzed with Cochran-Mantel–Haenszel test, with difference (95% CI) shown for no activity versus any activity.

† Manual muscle testing was assessed using the Medical Research Council score: for each individual muscle [range: 0 (no movement observed) to 5 (muscle contracts normally against full resistance).

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