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Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND

In patients undergoing mechanical ventilation for the acute respiratory distress syndrome (ARDS), neuromuscular blocking agents may improve oxygenation and decrease ventilator-induced lung injury but may also cause muscle weakness. We evaluated clinical outcomes after 2 days of therapy with neuromuscular blocking agents in patients with early, severe ARDS.

METHODS

In this multicenter, double-blind trial, 340 patients presenting to the intensive care unit (ICU) with an onset of severe ARDS within the previous 48 hours were randomly assigned to receive, for 48 hours, either cisatracurium besylate (178 patients) or placebo (162 patients). Severe ARDS was defined as a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FIO_2) of less than 150, with a positive end-expiratory pressure of 5 cm or more of water and a tidal volume of 6 to 8 ml per kilogram of predicted body weight. The primary outcome was the proportion of patients who died either before hospital discharge or within 90 days after study enrollment (i.e., the 90-day in-hospital mortality rate), adjusted for predefined covariates and baseline differences between groups with the use of a Cox model.

RESULTS

The hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, was 0.68 (95% confidence interval [CI], 0.48 to 0.98; P=0.04), after adjustment for both the baseline PaO_2:FIO_2 and plateau pressure and the Simplified Acute Physiology II score. The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group (P=0.08). Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo (P=0.05). The rate of ICU-acquired paresis did not differ significantly between the two groups.

CONCLUSIONS

In patients with severe ARDS, early administration of a neuromuscular blocking agent improved the adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness. (Funded by Assistance Publique–Hôpitaux de Marseille and the Programme Hospitalier de Recherche Clinique Régional 2004-26 of the French Ministry of Health; ClinicalTrials.gov number, NCT00299650.)

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The acute respiratory distress syndrome (ARDS) is characterized by hypoxemic respiratory failure; it affects both medical and surgical patients.[1] Despite rigorous physiological management,[2] in most studies, ARDS has been fatal in 40 to 60% of patients.[3-7]

Neuromuscular blocking agents are used in a large but highly variable proportion of patients with ARDS.[8-12] Current guidelines indicate that neuromuscular blocking agents are appropriate for facilitating mechanical ventilation when sedation alone is inadequate, most notably in patients with severe gas-exchange impairments.[10] In a four-center randomized, controlled trial of gas exchange in 56 patients with ARDS,[13] infusion of a neuromuscular blocking agent for a period of 48 hours was associated with improved oxygenation and a trend toward lower mortality in the intensive care unit (ICU) (46%, vs. 71% among patients who did not receive a blocking agent; P=0.06). However, this study was not designed or powered to evaluate mortality. Thus, the benefits and risks of adjunctive therapy with neuromuscular blocking agents in patients with ARDS who were receiving lung-protective mechanical ventilation[14] require further evaluation.

We conducted a multicenter, randomized, placebo-controlled, double-blind trial to determine whether a short period of treatment with the neuromuscular blocking agent cisatracurium besylate early in the course of severe ARDS would improve clinical outcomes.

Methods

Patients

Patients were enrolled from March 2006 through March 2008 at 20 ICUs in France (see the Appendix). Eligibility criteria were the receipt of endotracheal mechanical ventilation for acute hypoxemic respiratory failure and the presence of all of the following conditions for a period of no longer than 48 hours: ratio of the partial pressure of arterial oxygen (PaO_2, measured in millimeters of mercury) to the fraction of inspired oxygen (FIO_2, which is unitless) of less than 150 with the ventilator set to deliver a positive end-expiratory pressure of 5 cm of water or higher and a tidal volume of 6 to 8 ml per kilogram of predicted body weight, and bilateral pulmonary infiltrates that were consistent with edema. An additional eligibility criterion was the absence of clinical evidence of left atrial hypertension — that is, a pulmonary-capillary wedge pressure, if available, of less than 18 mm Hg. If the pulmonary-capillary wedge pressure was not available, echocardiography was performed if the patient had a history of, or risk factors for, ischemic heart disease or had crackles on auscultation. Exclusion criteria are listed in Figure 1.

The trial was monitored by an independent data and safety monitoring board. Randomization and blinding regarding the study-group assignments were performed according to Consolidated Standards for the Reporting of Trials (CONSORT) guidelines, as indicated in the Supplementary Appendix (available with the full text of this article at NEJM.org). The study protocol and statistical analysis plan (also available at NEJM.org) were approved for all centers by the ethics committee of the Marseille University Hospital (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale), according to French law. The study was conducted in accordance with the protocol and statistical analysis plan. Written informed consent was obtained from the patients or their proxies.

Study Treatment

Cisatracurium besylate (150-mg formulation, GlaxoSmithKline) and placebo were prepared in identical separate 30-ml vials for intravenous infusion. Peripheral-nerve stimulators were not permitted. The Ramsay sedation scale was used to adapt sedative requirements. The scale assigns the conscious state a score of 1 (anxious, agitated, or restless) to 6 (no response on glabellar tap). Once the assigned Ramsay sedation score was 6 and the ventilator settings were adjusted (Table 1), a 3-ml rapid intravenous infusion of 15 mg of cisatracurium besylate or placebo was administered, followed by a continuous infusion of 37.5 mg per hour for 48 hours. This regimen was based on the results of two studies of a total of 92 patients monitored for paralysis.[13,15]

Ventilation and Weaning Protocol

The volume assist–control mode of ventilation was used, with a tidal volume of 6 to 8 ml per kilogram of predicted body weight (Table 1). The goal was a saturation of peripheral blood oxygen (SpO_2) as measured by means of pulse oximetry of 88 to 95% or a PaO_2 of 55 to 80 mm Hg. To achieve this goal, FIO_2 and the positive end-expiratory pres-

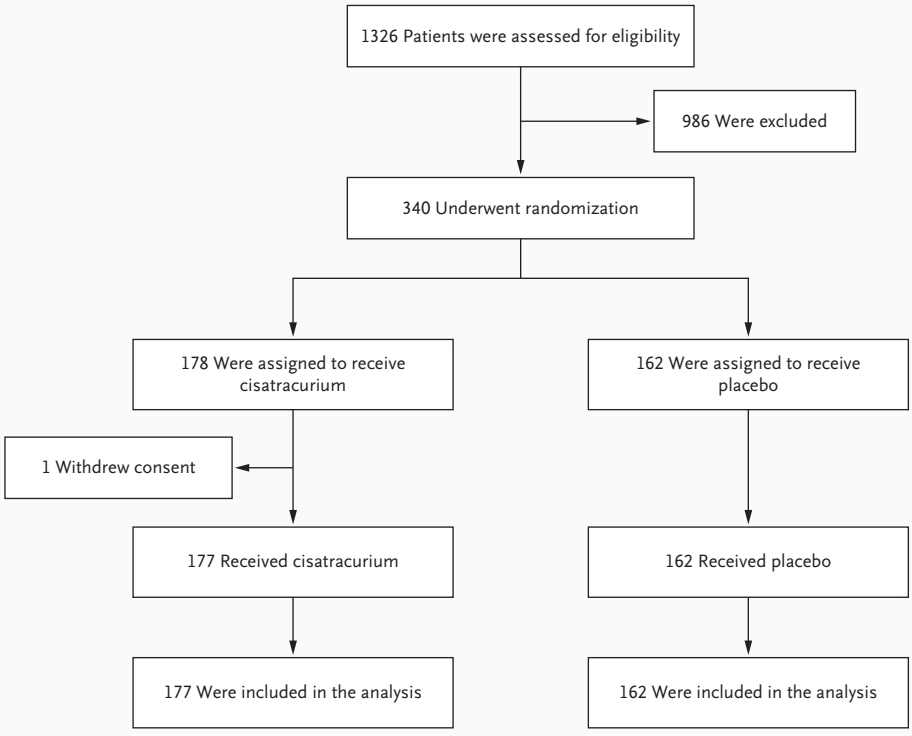

Figure 1. Randomization and Follow-up of the Patients, According to Study Group.

For the 986 patients who were assessed for eligibility but excluded, the reasons for exclusion were as follows: age younger than 18 years (19 patients, 1.9%), lack of consent (185 patients, 18.8%), continuous infusion of a neuromuscular blocking agent at enrollment (42 patients, 4.3%), known pregnancy (19 patients, 1.9%), enrollment in another trial within the previous 30 days, (57 patients, 5.8%), increased intracranial pressure (18 patients, 1.8%), severe chronic respiratory disease requiring long-term oxygen therapy or mechanical ventilation at home (95 patients, 9.6%), actual body weight exceeding 1 kg per centimeter of height, (20 patients, 2.0%), severe chronic liver disease (Child–Pugh class C) (82 patients, 8.3%), bone marrow transplantation or chemotherapy-induced neutropenia (97 patients, 9.8%), pneumothorax (18 patients, 1.8%), expected duration of mechanical ventilation of less than 48 hours (15 patients, 1.5%), decision to withhold life-sustaining treatment (168 patients, 17.0%), other reason (103 patients, 10.4%), and time window missed (48 patients, 4.9%).

sure were adjusted as in the Prospective, Randomized, Multi-Center Trial of 12 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome (ARMA).[14]

An open-label, rapid, intravenous injection of 20 mg of cisatracurium was allowed in both groups if the end-inspiratory plateau pressure remained greater than 32 cm of water for at least 10 minutes despite the administration of increasing doses of sedatives and decreasing tidal volume and positive end-expiratory pressure (if tolerated). If this rapid, intravenous injection resulted in a decrease of the end-inspiratory plateau pressure by less than 2 cm of water, a second injection of 20 mg of cisatracurium was allowed. If after the injection, the end-inspiratory plateau pressure did not decrease or decreased by less than 2 cm of water, cisatracurium was not administered again during the following 24-hour period.

ORGAN OR SYSTEM FAILURE

Patients were monitored daily for 28 days for signs of failure of nonpulmonary organs or systems.[14] Circulatory failure was defined as systolic blood pressure of 90 mm Hg or less or the need for vasopressor therapy. Coagulation failure was defined as a platelet count of 80,000 or less per cubic millimeter. Hepatic failure was defined as a serum bilirubin level of 2 mg per deciliter (34 μmol per liter) or higher. Renal failure was defined as a serum creatinine level of 2 mg per deciliter (177 μmol

Table 1. Summary of the Ventilation Procedure.*

Variable
Ventilator mode: volume assist–control
Initial tidal volume: 6–8 ml/kg of predicted body weight
Plateau pressure: ≤32 cm of water
Oxygenation goal: PaO_2 of 55–80 mm Hg or SpO_2 of 88–95%
Permitted combinations of FiO_2 and PEEP, respectively (cm of water): 0.3 and 5, 0.4 and 5, 0.4 and 8, 0.5 and 8, 0.5 and 10, 0.6 and 10, 0.7 and 10, 0.7 and 12, 0.7 and 14, 0.8 and 14, 0.9 and 14, 0.9 and 16, 0.9 and 18, 1.0 and 18, 1.0 and 20, 1.0 and 22, and 1.0 and 24
pH goal: 7.20–7.45
Procedure when oxygenation goal not achieved despite adjustments to FiO_2 and PEEP: use inhaled nitric oxide, almitrine mesylate, prone positioning, or any combination thereof
Procedure when plateau pressure is >32 cm of water for at least 10 min (in the following order, as needed): increase sedation, reduce tidal volume to 4 ml/kg, decrease PEEP by decrements of 2 cm of water, and perform injection of cisatracurium in a bolus of 20 mg (not to be given again if plateau pressure decreased by <2 cm of water because further doses would probably be futile, but permitted if the drug had its intended effect)
Procedure to correct hypercapnia when pH is <7.20 (in the following order, as needed): connect Y-piece directly to endotracheal tube, increase respiratory rate to a maximum of 35 cycles per min, and increase tidal volume to a maximum of 8 ml/kg
Weaning attempt: starting on day 3, if FiO_2 ≤0.6
Goals during weaning procedure: SpO_2 ≥88% and respiratory rate 26–35 cycles per min
Weaning procedure: decrease PEEP over 20–30 min to 5 cm of water
Pressure-support ventilation levels used during weaning procedure: 20, 15, 10, and 5 cm of water
If weaning procedure fails at a pressure-support ventilation level of 20 cm of water, switch to volume assist–control mode of ventilation
After at least 2 hr of successful pressure-support ventilation at a level of 5 cm of water, disconnect patient from the ventilator

* FiO_2 denotes fraction of inspired oxygen, PaO_2 partial pressure of arterial oxygen, PEEP positive end-expiratory pressure, and SpO_2 saturation of peripheral blood oxygen, as measured by means of pulse oximetry.

per liter) or higher. The number of days without organ or system failure was calculated by subtracting the number of days with organ failure from 28 days or from the number of days until death, if death occurred before day 28. Organs and systems were considered to be free of failure after hospital discharge. There was no recommendation regarding volume-resuscitation goals.

DATA COLLECTION

During the 24-hour period before randomization, we recorded data on demographic characteristics, physiological variables, relevant interventions performed in the ICU, radiographic findings, coexisting conditions, and medications. Data on ventilator settings, physiological variables, radiographic findings, and relevant therapeutic interventions were also recorded just before starting the study-drug infusion and again at 24, 48, 72, and 96 hours. Physiological variables were also measured daily between 6 a.m. and 10 a.m. until day 90 or until hospital discharge of a patient who could breath spontaneously.

Opioid doses were converted to morphine equivalents. The equivalencies were as follows: 0.01 mg of sufentanil=10 mg of morphine=0.1 mg of fentanyl=0.1 mg of remifentanil.[16]

Barotrauma was defined as newly developed pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele larger than 2 cm in diameter. Muscle strength was evaluated with the use of the Medical Research Council (MRC) scale, a previously validated scale that assesses three muscle groups in each arm and leg. The score for each muscle group can range from 0 (paralysis) to 5 (normal strength), with the overall score ranging from 0 to 60.[17] The definition of ICU-acquired paresis was an MRC score of less than 48.[17]

STUDY OUTCOMES

Primary Outcome

The primary outcome was the proportion of patients who died before hospital discharge and within 90 days after study enrollment (the 90-day mortality). Patients who were outside the hospital (including those in other types of health care facilities) and who were able to breathe spontaneously at day 90 were considered to have been discharged home. Because we anticipated that there would be an imbalance in at least one key risk factor at baseline, the primary outcome was derived from a Cox regression model in which we adjusted for such imbalance. We also report the crude mortality at day 90.

Secondary Outcomes

Secondary outcomes were the day-28 mortality, the numbers of days outside the ICU between day 1 and day 28 and between day 1 and day 90, the number of days without organ or system failure between day 1 and day 28, the rate of barotrauma, the rate of ICU-acquired paresis, the MRC scores on day 28 and at the time of ICU discharge, and the numbers of ventilator-free days (days since successful weaning from mechanical ventilation) between day 1 and day 28 and between day 1 and day 90. It was required that the patient breathe spontaneously,

without the aid of a ventilator, for a period of at least 48 hours for weaning from the ventilator to be considered successful. The number of ventilator-free days was considered to be zero for patients who were weaned from mechanical ventilation but who died before day 28 or day 90.[18]

STATISTICAL ANALYSIS

Assumptions for the sample-size calculation were based on our previous studies[13,15] that used the same inclusion criteria and on the European epidemiologic study Acute Lung Injury Verification (ALIVE).[4] Assuming a 50% mortality at 90 days in the placebo group, we calculated that 340 patients would need to be enrolled to detect a 15% absolute reduction in the 90-day mortality in the cisatracurium group as compared with the placebo group, with 80% statistical power and a two-sided alpha value of 0.05. No interim analysis was performed.

We assessed the differences between the groups using Student's t-test, the Wilcoxon test, the chi-square test, or Fisher's exact test, as appropriate. All reported P values are two-sided and have not been adjusted for multiple comparisons. Kaplan–Meier curves were plotted to assess the time from enrollment to death and the time to disconnection from the ventilator for a period of at least 48 hours.

The primary analysis consisted of evaluating the effect of cisatracurium on the primary outcome (i.e., 90-day mortality), with adjustment by means of a Cox multivariate proportional-hazards model that included two predefined covariates: the baseline Simplified Acute Physiology Score (SAPS) II and the baseline plateau pressure.[19] SAPS II is calculated from 12 physiological measurements during a 24-hour period, information about previous health status, and some information obtained at admission. This score ranges from 0 to 163, with higher scores indicating more severe disease. We planned to include all the variables for which there was an imbalance between the two groups at baseline, but the only imbalanced variable was the PaO_2:FIO_2 ratio. Therefore, we also conducted an analysis based on the baseline PaO_2:FIO_2 ratio, in which the two thirds of patients with a ratio below 120 (indicating hypoxemia) were compared with the third with a higher ratio. A total of 12 secondary analyses of prespecified outcomes were performed, and results of 9 of these are reported. Only one post hoc analysis was conducted; the results are reported.

RESULTS

BASELINE CHARACTERISTICS

We enrolled 340 patients, of whom 178 were randomly assigned to cisatracurium and 162 to placebo. We excluded 986 patients (Fig. 1). One patient in the cisatracurium group withdrew consent before treatment was started, and data for this patient were therefore not included in the analysis. The median time from the diagnosis of ARDS to study inclusion was 16 hours (interquartile range, 6 to 29) in the study population and did not differ significantly between the cisatracurium group (median, 18 hours; interquartile range, 6 to 31) and the placebo group (median, 15 hours; interquartile range, 7 to 27; P=0.45). The median time from initiation of mechanical ventilation to study inclusion did not differ significantly between the cisatracurium group (22 hours; interquartile range, 9 to 41) and the placebo group (21 hours; interquartile range, 10 to 42; P=0.91). The only significant difference between the two groups at baseline was a lower mean PaO_2:FIO_2 value in the cisatracurium group (P=0.03) (Table 2, and Table 1 in the Supplementary Appendix).

OUTCOMES

Primary Outcome

The Cox regression model yielded a hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, of 0.68 (95% confidence interval [CI], 0.48 to 0.98; P=0.04), after adjustment for the baseline PaO_2:FIO_2, SAPS II, and plateau pressure (Fig. 2). The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group (P=0.08).

Secondary Prespecified Outcomes

The beneficial effect of cisatracurium on the 90-day survival rate was confined to the two thirds of patients presenting with a PaO_2:FIO_2 ratio of less than 120. Among these patients, the 90-day mortality was 30.8% in the cisatracurium group and 44.6% in the control group (P=0.04) (Fig. 2 in the Supplementary Appendix). The absolute difference in 28-day mortality (mortality in the cisatracurium group minus mortality in the placebo group) was −9.6 percentage points (95% CI, −19.2 to −0.2; P=0.05) (Table 3).

The cisatracurium group had significantly more ventilator-free days than the placebo group during

Table 2. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic†	Cisatracurium (N=177)	Placebo N=162)	P Value
Age — yr	58±16	58±15	0.70
Tidal volume — ml/kg of predicted body weight	6.55±1.12	6.48±0.92	0.52
Minute ventilation — liters/min	10.0±2.5	10.1±2.2	0.83
PEEP applied — cm of water	9.2±3.2	9.2±3.5	0.87
Plateau pressure — cm of water	25.0±5.1	24.4±4.7	0.32
Respiratory-system compliance — ml/cm of water	31.5±11.6	31.9±10.7	0.71
FIO_2	0.79±0.19	0.77±0.20	0.33
PaO_2:FIO_2‡	106±36	115±41	0.03
pH	7.31±0.10	7.32±0.10	0.11
PaO_2 — mm Hg	80±24	85±28	0.09
$PaCO_2$ — mm Hg	47±11	47±11	0.62
Prone position or inhaled nitric oxide or almitrine mesylate — no. (%)	33 (18.6)	23 (14.2)	0.31
SAPS II§	50±16	47±14	0.15
Nonfatal condition according to McCabe–Jackson score — no. (%)¶	133 (75.1)	125 (77.2)	0.66
Main reason for ICU admission — no. (%)			
Medical	129 (72.9)	113 (69.8)	0.52
Surgical, emergency	27 (15.3)	31 (19.1)	0.34
Surgical, scheduled	21 (11.9)	18 (11.1)	0.83
Corticosteroids for septic shock — no. (%)	70 (39.5)	73 (45.1)	0.30
Direct lung injury — no. (%)	142 (80.2)	123 (75.9)	0.34

* Plus–minus values are means ±SD. FIO_2 denotes fraction of inspired oxygen, ICU intensive care unit, $PaCO_2$ partial pressure of arterial carbon dioxide, PEEP positive end-expiratory pressure, and SpO_2 saturation of peripheral oxygen as measured by means of pulse oximetry.
† All variables listed except age, nonfatal condition according to McCabe–Jackson score, and main reason for ICU admission were inclusion criteria.
‡ Partial pressure of arterial oxygen (PaO_2) was measured in millimeters of mercury.
§ The Simplified Acute Physiology Score (SAPS) II is calculated from 12 physiological measurements during a 24-hour period, information about previous health status, and some information obtained at admission. Scores can range from 0 to 163, with higher scores indicating more severe disease.
¶ Possible McCabe–Jackson scores for medical condition are 1 (nonfatal), 2 (ultimately fatal), and 3 (fatal).

the first 28 and 90 days (Table 3, and Fig. 3 in the Supplementary Appendix). The Cox regression model yielded an adjusted hazard ratio for weaning from mechanical ventilation by day 90, in the cisatracurium group as compared with the placebo group, of 1.41 (95% CI, 1.08 to 1.83; P=0.01). The cisatracurium group had more days free of failure of organs, other than the lungs, during the first 28 days (15.8±9.9 days, vs. 12.2±11.1 days in the placebo group; P=0.01). There were nearly significant between-group differences in the numbers of days without coagulation abnormalities, hepatic failure, and renal failure (Table 3). No patient required dialysis after hospital discharge during the first 28 days. Significantly more days were spent outside the ICU between day 1 and day 90 in the cisatracurium group.

Pneumothorax occurred in a larger proportion of patients in the placebo group (11.7%, vs. 4.0% in the cisatracurium group; P=0.01) and tended to develop earlier in the placebo group (Fig. 4 in the Supplementary Appendix). During the 48-hour period of study-drug infusion, pneumothorax occurred in one patient (0.6%) in the cisatracurium group as compared with eight patients (4.9%) in the placebo group (P=0.03). The plateau pressures and minute ventilations for the nine patients are presented in Table 5 in the Supplementary Appendix. Before the development of pneumothorax, none of these patients had an elevated plateau pressure necessitating changes in the mechanical-ventilation settings, changes in the sedation regimen, or open-label administration of cisatracurium.

The incidence of ICU-acquired paresis, as evaluated on the basis of the MRC score on day 28 or at the time of ICU discharge, did not differ significantly between the two groups (Table 3).

Secondary Post Hoc Outcome

Corticosteroids were used during the ICU stay in 189 patients. There was no significant effect of cisatracurium use on the 90-day mortality in the subgroup of patients given corticosteroids (Fig. 6 in the Supplementary Appendix).

VENTILATOR SETTINGS AND LUNG FUNCTION

Ventilator settings and lung-function variables during the first week are given in Table 7 in the Supplementary Appendix. On day 7, the PaO_2:FIO_2 ratio was higher, and the $PaCO_2$ value lower, in the cisatracurium group than in the placebo group.

COINTERVENTIONS

During the ICU stay, there were no significant between-group differences in the incidence of cointerventions. A total of 42% of patients in the cisatracurium group and 48% in the placebo group were treated with the use of prone positioning, inhaled nitric oxide, intravenous almitrine mesylate, or a combination of these (Table 8 in the Supplementary Appendix). The criteria for using these interventions were the same in the two groups.

Open-label cisatracurium was given more frequently in the placebo group than in the cisatracurium group during the first 48 hours after enrollment. However, the two groups did not differ significantly with respect to the number of patients given at least one open-label cisatracurium bolus during the entire ICU stay after enrollment (Table 8 in the Supplementary Appendix). The required dose of sedatives or analgesics was similar in the two groups during the first week of the study (Table 9 in the Supplementary Appendix).

SAFETY

Bradycardia developed during the cisatracurium infusion in one patient. No other side effects were reported.

DISCUSSION

Treatment with the neuromuscular blocking agent cisatracurium for 48 hours early in the course of severe ARDS improved the adjusted 90-day survival rate, increased the numbers of ventilator-free days and days outside the ICU, and decreased the incidence of barotrauma during the first 90 days. It did not significantly improve the overall 90-day mortality.

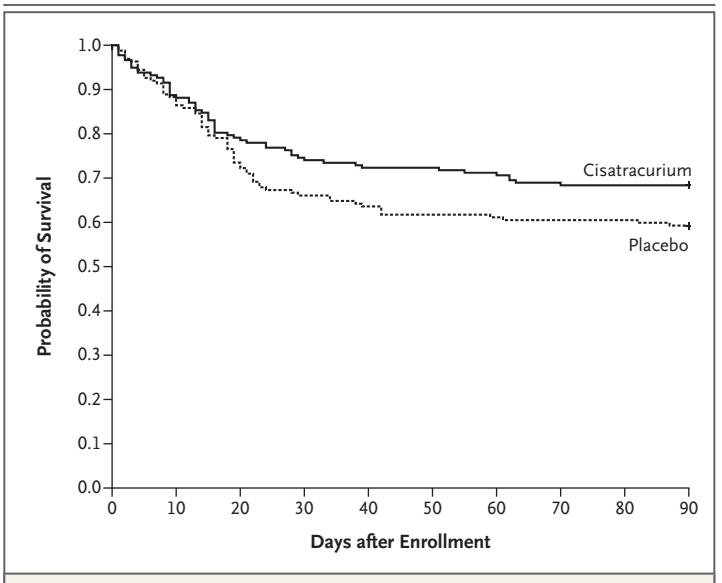

Figure 2. Probability of Survival through Day 90, According to Study Group.

Strengths of this trial include the methods used to minimize bias (blinded randomization assignments, a well-defined study protocol, complete follow-up, and intention-to-treat analyses). The recruitment of a large number of patients from 20 multidisciplinary ICUs where international standards of care are followed suggests that our data can be generalized to other ICUs.

Limitations of the trial include the fact that our results were obtained for cisatracurium besylate and may not apply to other neuromuscular blocking agents. Furthermore, we did not assess the use of a neuromuscular blocking agent late in the course of ARDS or use on the basis of plateau-pressure or transpulmonary-pressure measurements.[20] Another limitation is the absence of data on conditions known to antagonize or potentiate neuromuscular blockade. However, any condition that increases the duration of neuromuscular blockade would have adversely affected the patients receiving the neuromuscular blocking agent, in particular by increasing the duration of mechanical ventilation.

The sample-size calculation was based on our two previous studies performed in four ICUs[13,15] that used the same inclusion criteria as were used in the current trial and on the European epidemiologic study ALIVE.[4] However, the mortality in the placebo group in this study (40.7%) is lower than

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

* Plus–minus values are means ±SD. ICU denotes intensive care unit, and IQR interquartile range.
† The number of ventilator-free days was defined as the number of days since successful weaning from mechanical ventilation after a period of spontaneous breathing lasting at least 48 consecutive hours.
‡ Barotrauma was defined as any new pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele larger than 2 cm in diameter.
§ The Medical Research Council (MRC) scale is a previously validated scale that assesses strength in three muscle groups in each arm and leg. The score for each muscle group can range from 0 (paralysis) to 5 (normal strength), with the overall score ranging from 0 to 60.[17]
¶ ICU-acquired paresis was defined as an overall MRC score of less than 48.

that in the control groups in the earlier studies. Given the observed mortality in our placebo group, the current study was underpowered. Indeed, 885 patients would have been needed to be enrolled to achieve 80% statistical power with a two-sided alpha value of 0.05.

Finally, all our patients had severe ARDS. Additional work is needed to determine whether the use of neuromuscular blocking agents for only 24 hours is beneficial in selected patients. In our general analysis, which was prespecified but with post hoc determination of the threshold value for classifying subgroups, we found that the beneficial effect of the neuromuscular blocking agent on survival was confined to the two thirds of patients with a PaO_2:FIO_2 ratio below 120.

The mechanisms underlying the beneficial effect of neuromuscular blocking agents remain speculative. A brief period of paralysis early in the course of ARDS may facilitate lung-protective mechanical ventilation by improving patient–ventilator synchrony and allowing for the accurate adjustment of tidal volume and pressure levels, thereby limiting the risk of both asynchrony-related alveolar collapse and regional alveolar-pressure increases with overdistention. Another possible mechanism of the benefit involves a decrease in lung or systemic inflammation.[15]

The main safety concern with the use of a neuromuscular blocking agent is muscle weakness; the risk varies among agents.[21,22] Steroidal compounds (vecuronium, pancuronium, and rocuronium) may carry the highest risk of myopathy,[23] although myopathy has also been reported with benzylisoquinolines, including cisatracurium besylate.[24,25] Muscle weakness was not increased significantly by the use of the neuromuscular blocking agent in our study. The short duration of use of the neuromuscular blocking agent probably explains this result.

In conclusion, this multicenter trial provides evidence that the administration of a neuromuscular blocking agent early in the course of severe ARDS managed with low-tidal-volume ventilation may improve outcomes. Future studies are needed to replicate and expand these findings before they can be widely adopted in clinical practice.

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APPENDIX

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