An Observational Study of the Efficacy of Cisatracurium Compared with Vecuronium in Patients with or at Risk for Acute Respiratory Distress Syndrome

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Abstract

Rationale: The neuromuscular blocking agent cisatracurium may improve mortality for patients with moderate-to-severe acute respiratory distress syndrome (ARDS). Other neuromuscular blocking agents, such as vecuronium, are commonly used and have different mechanisms of action, side effects, cost, and availability in the setting of drug shortages.

Objectives: To determine whether cisatracurium is associated with improved outcomes when compared with vecuronium in patients at risk for and with ARDS.

Methods: Using a nationally representative database, patients who were admitted to the ICU with a diagnosis of ARDS or an ARDS risk factor, received mechanical ventilation, and were treated with a continuous infusion of neuromuscular blocking agent for at least 2 days within 2 days of hospital admission were included. Patients were stratified into two groups: those who received cisatracurium or vecuronium. Propensity matching was used to balance both

patient- and hospital-specific factors. Outcomes included hospital mortality, duration of mechanical ventilation, ICU and hospital duration, and discharge location.

Measurements and Main Results: Propensity matching successfully balanced all covariates for 3,802 patients (1,901 per group). There was no significant difference in mortality (odds ratio, 0.932; $P = 0.40$) or hospital days (-0.66 d; $P = 0.411$) between groups. However, patients treated with cisatracurium had fewer ventilator days (-1.01 d; $P = 0.005$) and ICU days (-0.98 d; $P = 0.028$) but were equally likely to be discharged home (odds ratio, 1.19; $P = 0.056$).

Conclusions: When compared with vecuronium, cisatracurium was not associated with a difference in mortality but was associated with improvements in other clinically important outcomes. These data suggest that cisatracurium may be the preferred neuromuscular blocking agent for patients at risk for and with ARDS.

Keywords: acute respiratory distress syndrome; mechanical ventilators; neuromuscular blockade; patient outcome assessment

Despite more than 50 years of research, the mortality from acute respiratory distress syndrome (ARDS) remains unacceptably high (1). Importantly, mechanical

ventilation can cause injury to the lung—termed *ventilator-induced lung injury*—in patients with and at risk for ARDS. In patients at risk for ARDS, ventilator-

induced lung injury can increase the likelihood of developing ARDS and ultimately increase mortality. Ventilator-induced lung injury can be caused by both

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At a Glance Commentary

Scientific Knowledge on the

Subject: In patients at risk for and with acute respiratory distress syndrome (ARDS), mechanical ventilation can cause injury to the lung. Neuromuscular blocking agents may be used to improve oxygenation, decrease ventilatory dyssynchrony, and reduce ventilator-induced lung injury. The neuromuscular blocking agent cisatracurium may improve mortality for patients with moderate-to-severe ARDS. However, it is unknown whether the potential benefits of cisatracurium would be observed with other neuromuscular blocking agents.

What This Study Adds to the

Field: When compared with vecuronium, cisatracurium was not associated with a difference in mortality but was associated with a significant reduction in ventilator days and ICU days. These data suggest that cisatracurium may be the preferred neuromuscular blockade agent for patients at risk for and with ARDS.

large tidal volume and high-pressure ventilation (2). One treatment to minimize ventilator-induced lung injury is low-tidal volume mechanical ventilation of 6 ml/kg ideal body weight. Low tidal volume ventilation reduced mortality in patients with ARDS and reduced pulmonary complications in those at risk for ARDS (3–7). However, low tidal volume ventilation alone does not eliminate the development of ventilator-induced lung injury, and patients may continue to generate both high pressure and large tidal volume through spontaneous efforts. Consequently, methods to prevent such patient–ventilator interactions—termed *patient self-inflicted lung injury*—and thus reduce the propagation of ventilator-induced lung injury are under active investigation to both prevent and treat ARDS (8).

In patients at risk for and with ARDS, neuromuscular blockade may be used to improve oxygenation, eliminate patient–ventilator interactions, decrease ventilatory dyssynchrony, and reduce ventilator-induced lung injury. A clinical trial of a 48-hour infusion of cisatracurium

(initiated within the first 48 h of mechanical ventilation) in patients with moderate to severe ARDS suggested that neuromuscular blockade may improve outcomes in patients with ARDS (9). Neuromuscular blockade is generally thought to improve outcomes by reducing ventilator-induced lung injury. In addition, cisatracurium metabolism does not depend on renal or hepatic function—which may increase its use in patients with multiorgan dysfunction and an increased risk of death. In addition, the chemical structure of cisatracurium may reduce the risk of ICU-associated weakness when compared with other neuromuscular blockade agents (10). Consequently, other neuromuscular blockade agents may not have the same potential beneficial effects on patient outcomes.

We conducted a multicenter, observational study in patients with and at risk for ARDS to determine whether patients treated with cisatracurium or vecuronium, another commonly used neuromuscular blockade agent, had similar outcomes. Determining whether the beneficial effects of neuromuscular blockade are specific to cisatracurium is important for several reasons. First, differences in patient outcomes could be explained by mechanistic differences in neuromuscular blockade function or by the side-effect profiles of different agents. Second, these results will determine whether the potentially beneficial effects of cisatracurium balance its nearly threefold increase in cost over vecuronium (11). Finally, if the beneficial effects of cisatracurium are similar to those of vecuronium, then the use of vecuronium can be supported in the setting of drug shortages that have occurred with cisatracurium.

Methods

Study Design

We performed a multicenter, observational cohort study of the Premier Incorporated Perspective Database, a cohort of more than 5.4 million unique ICU admissions nationally from January 2010 through December 2014. The database has been described in detail previously (12–15). The Colorado Multiple Institutional Review Board approved this study (#16-0505).

Patient Population

Mechanically ventilated, ICU patients with a diagnosis of ARDS or a known ARDS risk

factor and who received at least 2 days of a continuous infusion of neuromuscular blockade within the first 2 days of hospital admission were included. ARDS risk factors included acute hypoxemic respiratory failure, pneumonia, sepsis, trauma, burns, and other diagnoses or treatments (i.e., multiple transfusions) (16). Patients with ARDS risk factors were included because of the underdiagnosis of ARDS and the potential benefit of decreasing ventilator-induced lung injury, reducing the development of ARDS, and minimizing other pulmonary complications in these patients (17). Patient diagnosis was determined on the basis of the *International Classification of Disease Codes, Ninth Revision, Clinical Modification* (ICD-9-CM) (additional details may be found in Table E1 in the online supplement) (18). To minimize unmeasured confounding by worsening severity of illness after admission, and based on previous clinical trials, patients were included if they received at least two consecutive days of either cisatracurium or vecuronium by continuous intravenous infusions, exclusively, within 48 hours of hospital admission (9). Vecuronium was selected as it was the second most commonly used neuromuscular blockade agent in the Premier database. Other agents, including atracurium (1,533 patients) and pancuronium (1,271 patients), were less frequently utilized as continuous infusions.

Outcomes

The following outcome measures were determined: hospital mortality, ventilator days, ICU days, hospital days, and discharge home versus elsewhere.

Data Analysis

Statistical analysis was performed using previously published methodology with modifications to include variables pertinent to this study (19). Patient characteristics included age; sex; the diagnosis of ARDS, pneumonia, chronic obstructive pulmonary disease (COPD), disseminated intravascular coagulation (DIC), acute liver failure, sepsis, septic shock; the Elixhauser comorbidity index; and the year and quarter of admission. The Elixhauser index is a comprehensive set of 30 comorbidities that correlate with patient outcomes when hospitalized (20). We ensured that the diagnosis of pneumonia, ARDS, DIC, liver failure, sepsis, septic shock, cancer, or COPD was present at the time of

admission. Finally, the numbers of vasopressor days, renal failure days, and mechanical ventilation days before the initiation of neuromuscular blockade were included. Hospital characteristics included the following: hospital region, hospital size, rural versus urban status, and teaching versus nonteaching status. Urban status and teaching status of each hospital was defined according to the Premier database. These data were compared between groups, using the χ^2 test for categorical data and the unpaired *t* test or Kruskal-Wallis test for continuous variables.

A nonparsimonious regression model was used to produce a propensity score for treatment with vecuronium, using the hospital and patient characteristics described above. For the propensity-matched analysis (primary analysis), each patient in the vecuronium group was matched 1:1 with a patient in the cisatracurium group to the nearest third decimal point, using a nearest neighbor algorithm (21). We chose to match to the third decimal point (caliper 0.001) because it was less than the commonly suggested 0.2 SD of the propensity score logit, resulting in both reasonable matches and good overall sample size. Final models included each hospital as a random effect and all patient and hospital characteristics used to calculate the propensity score. In addition, multivariable regression modeling, including all patient and hospital characteristics used to calculate the propensity score, was used to confirm these findings (secondary analysis). Finally, to assess whether hospitals that use only cisatracurium or vecuronium alone may disproportionately influence outcomes, a sensitivity analysis stratified by hospitals that use cisatracurium alone, vecuronium alone, or both agents was performed. All analysis was performed in SAS 9.4 (SAS Institute Inc.). Some of the results of these studies have been previously reported in the form of an abstract at the 2017 American Thoracic Society Meeting (22).

Results

Of more than 5.4 million ICU admissions, 1.45 million required 48 hours of mechanical ventilation. Of these, a total of 13,436 patients were identified who received either cisatracurium or vecuronium for at least 48 hours, of which 6,925 patients received neuromuscular blockade within

48 hours of admission. All patients had at least one ARDS risk factor; 6,208 patients had acute hypoxemic respiratory failure, 2,509 patients had pneumonia, 2,154 patients had sepsis, 849 patients had trauma, and 116 patients had burns. A total of 512 patients received an ICD-9-CM diagnosis code for ARDS (Figure 1).

A total of 4,735 patients received cisatracurium and 2,190 patients received vecuronium. Overall, patients in the cisatracurium group were older (mean $\pm$ SD, 54.3 $\pm$ 16.2 vs. 50.8 $\pm$ 17.1 yr; $P < 0.001$) and more likely female (34.7 vs. 28.7%; $P < 0.001$) compared with the vecuronium group. At hospital admission, patients in the cisatracurium group had increased rates of pneumonia (37.6 vs. 33.4%; $P = 0.001$) but were less likely to have ARDS (5.7 vs. 11.0%; $P < 0.001$) when compared with the vecuronium group (Table 1). However, patients in the cisatracurium group were more likely to have severe sepsis (20.1 vs. 12.4%; $P < 0.001$), septic shock (15.7 vs. 8.5%; $P < 0.001$), liver disease (14.2 vs. 10.4%; $P < 0.001$), and a greater number of Elixhauser comorbidities (median [interquartile range], 11.0 [5–18] vs. 9.0 [2–16]; $P < 0.001$) when compared with the vecuronium group at hospital admission. Patients in the cisatracurium group received more days of neuromuscular

blockade (3.3 vs. 3.1 d; $P = 0.003$) than those receiving vecuronium.

Propensity-Matched Analysis (Primary Analysis)

After propensity matching 86% of patients in the vecuronium group were successfully matched 1:1 with an equal number of patients in the cisatracurium group, yielding a total of 1,901 patients in each group. Diagnostic evaluation of the propensity matching is included in the online supplement (Table E2 and Figures E1–E3). Propensity matching eliminated differences between admission patient and hospital characteristics and reduced differences in patient characteristics at discharge (Table 2). After propensity matching, patients in the cisatracurium group received more days of neuromuscular blockade when compared with those in the vecuronium group (3.2 vs. 3.0 d; $P = 0.002$).

In a fully adjusted, propensity-matched model, patients treated with cisatracurium experienced no difference in mortality (odds ratio [OR], 0.93; 95% confidence interval [CI], 0.79–1.10; $P = 0.40$) or hospital length of stay (OR, 0.66; 95% CI, –0.75 to 1.83; $P = 0.41$) compared with patients treated with vecuronium. However, patients treated with cisatracurium experienced fewer ventilator days (OR, 1.01; 95% CI, 0.30–1.72; $P = 0.005$) and fewer ICU days

Figure 1. Inclusion flow diagram. ARDS = acute respiratory distress syndrome.

Table 1. Baseline Covariates of Entire Study Population before Propensity Matching

	All Subjects (N = 6,925)	Cisatracurium (n = 4,735)	Vecuronium (n = 2,190)	P Value	Standardized Mean Difference
Age, yr	53.2 (16.60)	54.3 (16.24)	50.8 (17.10)	<0.001	−0.2112
Sex	2,270 (32.8%)	1,642 (34.7%)	628 (28.7%)	<0.001	−0.1293
Race					
White	4,624 (66.8%)	3,103 (65.5%)	1,521 (69.5%)	<0.001	0.1351
Black	986 (14.2%)	675 (14.3%)	311 (14.2%)		
Hispanic	84 (1.2%)	47 (1.0%)	37 (1.7%)		
Other	1,231 (17.8%)	910 (19.2%)	321 (14.7%)		
Admission year*					
2010	1,024 (14.8%)	556 (11.7%)	468 (21.3%)	<0.001	0.4363
2011	1,373 (19.8%)	879 (18.5%)	494 (22.7%)		
2012	1,535 (22.2%)	1,025 (21.6%)	510 (23.3%)		
2013	1,630 (23.5%)	1,154 (24.5%)	476 (21.7%)		
2014	1,363 (19.7%)	1,121 (23.7%)	242 (11.0%)		
Patient characteristics before initiation of neuromuscular blockade					
Acute respiratory distress syndrome	512 (7.4%)	271 (5.7%)	241 (11.0%)	<0.001	0.1916
Pneumonia	2,509 (36.2%)	1,778 (37.6%)	731 (33.4%)	0.001	−0.0873
Severe sepsis	1,224 (17.7%)	953 (20.1%)	271 (12.4%)	<0.001	−0.2113
Septic shock	930 (13.4%)	743 (15.7%)	187 (8.5%)	<0.001	−0.2205
Liver disease	898 (13.0%)	671 (14.2%)	227 (10.4%)	<0.001	−0.1162
DIC syndrome	110 (1.6%)	85 (1.8%)	25 (1.1%)	0.045	−0.0544
COPD	1,329 (19.2%)	945 (20.0%)	384 (17.5%)	0.017	−0.0621
Metastatic cancer	107 (1.5%)	77 (1.6%)	30 (1.4%)	0.422	−0.0211
Elixhauser comorbidities (count)	11.0 (4–18)	11.0 (5–18)	9.0 (2–16)	<0.001	−0.2249
Days needing mechanical ventilation before neuromuscular blockade	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	0.977	−0.0007
Days needing vasopressors before neuromuscular blockade	1.0 (0–3)	1.0 (0–3)	1.0 (0–3)	0.019	−0.0598
Days with renal failure before neuromuscular blockade	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	<0.001	−0.1102
Patient characteristics at discharge					
Acute respiratory distress syndrome	921 (13.3%)	558 (11.8%)	363 (16.6%)	<0.001	0.1377
Pneumonia	3,882 (56.1%)	2,642 (55.8%)	1,240 (56.6%)	0.521	0.0166
Severe sepsis	1,656 (23.9%)	1,263 (26.7%)	393 (17.9%)	<0.001	−0.2108
Septic shock	1,274 (18.4%)	1,004 (21.2%)	270 (12.3%)	<0.001	−0.2393
Liver disease	1,281 (18.5%)	959 (20.3%)	322 (14.7%)	<0.001	−0.1465
DIC syndrome	235 (3.4%)	181 (3.8%)	54 (2.5%)	0.004	−0.0778
COPD	1,369 (19.8%)	971 (20.5%)	398 (18.2%)	0.024	−0.0591
Metastatic cancer	107 (1.5%)	77 (1.6%)	30 (1.4%)	0.422	−0.0211
Delirium/encephalopathy	920 (13.3%)	687 (14.5%)	233 (10.6%)	<0.001	−0.1169
Critical illness myopathy/neuropathy	141 (2.0%)	111 (2.3%)	30 (1.4%)	0.008	−0.0722
Days needing vasopressors	2.0 (1–4)	2.0 (1–4)	2.0 (0–4)	<0.001	−0.1196
Days with renal failure	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	<0.001	−0.1608
Hospital characteristics					
Number of beds					
<200	590 (8.5%)	441 (9.3%)	149 (6.8%)	<0.001	0.2055
200–300	815 (11.8%)	523 (11.0%)	292 (13.3%)		
301–400	1,671 (24.1%)	1,223 (25.8%)	448 (20.5%)		
401–500	1,299 (18.8%)	918 (19.4%)	381 (17.4%)		
>500	2,550 (36.8%)	1,630 (34.4%)	920 (42.0%)		
Teaching					
No	3,075 (44.4%)	2,207 (46.6%)	868 (39.6%)	<0.001	0.1412
Yes	3,850 (55.6%)	2,528 (53.4%)	1,322 (60.4%)		
Urban/rural					
Rural	471 (6.8%)	322 (6.8%)	149 (6.8%)	0.996	−0.0001
Urban	6,454 (93.2%)	4,413 (93.2%)	2,041 (93.2%)		
Provider region					
Midwest	1,424 (20.6%)	951 (20.1%)	473 (21.6%)	<0.001	0.3296
Northeast	1,001 (14.5%)	689 (14.6%)	312 (14.2%)		
South	3,445 (49.7%)	2,541 (53.7%)	904 (41.3%)		
West	1,055 (15.2%)	554 (11.7%)	501 (22.9%)		

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; DIC = disseminated intravascular coagulopathy. Data are presented as mean (SD), *n* (%), or median (interquartile range).

*Although the actual match was performed by year and quarter, only yearly data are shown here for ease of presentation.

Table 2. Values of Covariates after Propensity Matching in Matched Patients

	All Subjects (N = 3,802)	Cisatracurium (n = 1,901)	Vecuronium (n = 1,901)	P Value	Standardized Mean Difference
Age, yr	51.9 (16.80)	52.0 (16.76)	51.9 (16.84)	0.837	−0.0067
Female	1,160 (30.5%)	579 (30.5%)	581 (30.6%)	0.944	0.0023
Race					
White	2,540 (66.8%)	1,207 (63.5%)	1,333 (70.1%)	<0.001	0.2445
Black	515 (13.5%)	236 (2.4%)	279 (14.7%)		
Hispanic	48 (1.3%)	20 (1.1%)	28 (1.5%)		
Other	699 (18.4%)	438 (23.0%)	261 (13.7%)		
Admission year*					
2010	689 (18.1%)	357 (18.8%)	332 (17.4%)	0.999	0.0764
2011	848 (22.3%)	424 (22.3%)	424 (22.3%)		
2012	890 (23.4%)	433 (22.8%)	457 (24.1%)		
2013	883 (23.3%)	434 (22.8%)	449 (23.6%)		
2014	492 (12.9%)	253 (13.3%)	239 (12.6%)		
Patient characteristics before initiation of neuromuscular blockade					
Acute respiratory distress syndrome	336 (8.8%)	171 (9.0%)	165 (8.7%)	0.732	−0.0111
Pneumonia	1,321 (34.7%)	654 (34.4%)	667 (35.1%)	0.658	0.0144
Severe sepsis	534 (14.0%)	269 (14.2%)	265 (13.9%)	0.852	−0.0061
Septic shock	378 (9.9%)	192 (10.1%)	186 (9.8%)	0.745	−0.0105
Liver disease	443 (11.7%)	227 (11.9%)	216 (11.4%)	0.578	−0.0180
DIC syndrome	45 (1.2%)	22 (1.2%)	23 (1.2%)	0.881	0.0049
COPD	704 (18.5%)	347 (18.3%)	357 (18.8%)	0.676	0.0135
Metastatic cancer	62 (1.6%)	32 (1.7%)	30 (1.6%)	0.798	−0.0083
Elixhauser comorbidities (count)	10.0 (3–16)	10.0 (3–16)	10.0 (3–17)	0.586	0.0177
Days needing mechanical ventilation before neuromuscular blockade	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	0.545	0.0196
Days needing vasopressors before neuromuscular blockade	1.0 (0–3)	1.0 (0–3)	1.0 (0–3)	0.657	0.0143
Days with renal failure before neuromuscular blockade	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	0.679	0.0134
Patient characteristics at discharge					
Acute respiratory distress syndrome	564 (14.8%)	294 (15.5%)	270 (14.2%)	0.274	−0.0355
Pneumonia	2,108 (55.4%)	1,017 (53.5%)	1,091 (57.4%)	0.016	0.0784
Severe sepsis	774 (20.4%)	411 (21.6%)	363 (19.1%)	0.053	−0.0627
Septic shock	545 (14.3%)	292 (15.4%)	253 (13.3%)	0.071	−0.0586
Liver disease	643 (16.9%)	340 (17.9%)	303 (15.9%)	0.110	−0.0519
DIC syndrome	111 (2.9%)	59 (3.1%)	52 (2.7%)	0.500	−0.0219
COPD	729 (19.2%)	358 (18.8%)	371 (19.5%)	0.592	0.0174
Metastatic cancer	62 (1.6%)	32 (1.7%)	30 (1.6%)	0.798	−0.0083
Delirium/encephalopathy	485 (12.8%)	268 (14.1%)	217 (11.4%)	0.013	−0.0805
Critical illness myopathy/neuropathy	68 (1.8%)	42 (2.2%)	26 (1.4%)	0.052	−0.0635
Days needing vasopressors	2.0 (1–4)	2.0 (1–4)	2.0 (1–4)	0.057	−0.0617
Days with renal failure	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	0.040	−0.0665
Hospital characteristics					
Number of beds					
<200	257 (6.8%)	123 (6.5%)	134 (7.0%)	0.898	0.0337
200–300	485 (12.8%)	240 (12.6%)	245 (12.9%)		
301–400	809 (21.3%)	415 (21.8%)	394 (20.7%)		
401–500	696 (18.3%)	347 (18.3%)	349 (18.4%)		
>500	1,555 (40.9%)	776 (40.8%)	779 (41.0%)		
Teaching					
No	1,512 (39.8%)	753 (39.6%)	759 (39.9%)	0.842	−0.0064
Yes	2,290 (60.2%)	1,148 (60.4%)	1,142 (60.1%)		
Urban/rural					
Rural	274 (7.2%)	137 (7.2%)	137 (7.2%)	1.000	0.0000
Urban	3,528 (92.8%)	1,764 (92.8%)	1,764 (92.8%)		
Provider region					
Midwest	765 (20.1%)	370 (19.5%)	395 (20.8%)	0.780	0.0338
Northeast	551 (14.5%)	277 (14.6%)	274 (14.4%)		
South	1,743 (45.8%)	882 (46.4%)	861 (45.3%)		
West	743 (19.5%)	372 (19.6%)	371 (19.5%)		

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; DIC = disseminated intravascular coagulopathy.

Data are presented as mean (SD), n (%), or median (interquartile range).

*While the actual match was performed by year and quarter, only yearly data are shown here for ease of presentation.

(OR, 0.98; 95% CI, 0.11–1.86; $P = 0.028$) compared with patients treated with vecuronium. Moreover, patients who were treated with cisatracurium were equally likely to be discharged home as patients treated with vecuronium (OR, 1.19; 95% CI, 1.00–1.43; $P = 0.056$) (Table 3). There were no significant differences in outcomes between hospitals that used only cisatracurium, only vecuronium, or both agents (*see the online supplement*).

Multivariable Analysis of the Entire Cohort

The entire cohort (6,925 patients) was then analyzed using multivariable regression after adjusting for differences in the same patient and hospital characteristic used to calculate the propensity score. This multivariable analysis demonstrated that patients treated with cisatracurium experienced no difference in mortality rate when compared with patients treated with vecuronium (OR, 0.91; 95% CI, 0.80–1.02; $P = 0.11$). However, patients treated with cisatracurium experienced fewer ventilator days (0.78; 95% CI, 0.31–1.25; $P = 0.001$), fewer ICU days (0.73; 95% CI, 0.17–1.30; $P = 0.011$), but similar hospital days (0.57; 95% CI, –0.29 to 1.44; $P = 0.05$) than patients treated with vecuronium. Finally, patients who were treated with cisatracurium experienced an increased likelihood to be discharged home than patients treated with vecuronium (OR, 1.19; 95% CI, 1.05–1.37; $P = 0.008$) (Table 3).

Discussion

We performed a multicenter, observational cohort study to assess outcomes in patients at risk for or with ARDS who were treated with cisatracurium or vecuronium infusions. We demonstrated that there was no significant association between mortality

or length of hospitalization and treatment with cisatracurium or vecuronium. However, there was an association of fewer ventilator days and ICU days between patients treated with cisatracurium and patients treated with vecuronium. Patients who survived to hospital discharge and were treated with cisatracurium were not significantly more likely to be discharged home than patients treated with vecuronium in the propensity-matched model, but were more likely to be discharged home in the linear regression model.

A prior randomized control trial demonstrated that a 48-hour infusion of cisatracurium within the first 48 hours of mechanical ventilation improved 90-day adjusted mortality, and decreased ventilator days and ICU days, in patients with moderate-to-severe ARDS when compared with placebo (9). In a separate study, the use of cisatracurium was associated with decreased markers of inflammation in both bronchial alveolar lavage and serum in patients with ARDS compared with placebo (23). Similarly, Steingrub and colleagues demonstrated that treatment with any neuromuscular blockade agent was associated with reduced mortality in patient with pulmonary sepsis when compared with usual care (24). However, it remained unclear whether these results were specific to cisatracurium alone, or could be generalizable to other neuromuscular blockade agents. Our findings suggest that cisatracurium is at least equal to and may be superior to vecuronium, another commonly used neuromuscular blockade agent.

There are multiple mechanisms by which neuromuscular blockade agents may decrease ventilator-induced lung injury and thus improve mortality. At least three mechanisms generalizable to all neuromuscular blockade agents have been proposed to explain this trend

toward improvement in mortality with neuromuscular blockade (25). First, neuromuscular blockade may eliminate ventilator dyssynchrony and therefore reduce ventilator-induced lung injury. Second, by decreasing oxygen consumption by muscular activity and improving systemic oxygenation, neuromuscular blockade could reduce respiratory demand and cardiac output. Decreasing respiratory demand may decrease ventilator-induced lung injury from high minute ventilation. Decreasing cardiac output may decrease ventilator-induced lung injury from pulmonary vascular strain. Third, neuromuscular blockade may reduce atelectrauma by reducing pulmonary derecruitment with spontaneous breathing.

Cisatracurium may improve outcomes over vecuronium through additional mechanisms not directly related to reducing ventilator-induced lung injury. First, cisatracurium is cleared by Hofmann elimination; a mechanism that is independent of renal or hepatic function (10). Other neuromuscular blockade agents rely on primarily renal or hepatic clearance and thus are more slowly eliminated in critically ill patients, even without other organ failure (26). Thus, these other neuromuscular blockade agents may have continued effect after the infusion has been stopped, potentially increasing the need for sedation and mechanical ventilation. Second, the chemical structure of cisatracurium (a benzyliisoquinolinium) may decrease the risk of ICU-associated weakness when compared with other neuromuscular blockade agents (aminosteroids) (10). ICU-associated weakness results in prolonged physical rehabilitation, and decreased quality of life in survivors (27).

In this context, our findings add information to the clinical management of ARDS. Despite the cohort of patients who

Table 3. Results of Propensity-Matched and Multivariate Analysis in Patients with or at Risk for Acute Respiratory Distress Syndrome

	Propensity-Matched Analysis ($N = 3,802$)			Multivariable Analysis ($N = 6,925$)		
	Estimate	95% CI	P Value	Estimate	95% CI	P Value
Odds of mortality, OR	0.93	0.79 to 1.10	0.40	0.91	0.80 to 1.02	0.11
Difference in ventilator days	1.01	0.30 to 1.72	0.005	0.78	0.31 to 1.25	0.001
Difference in ICU days	0.98	0.11 to 1.86	0.028	0.73	0.17 to 1.30	0.011
Difference in hospital days	0.66	–0.75 to 1.83	0.41	0.57	–0.29 to 1.44	0.05
Odds of discharge to home, OR	1.19	1.00 to 1.43	0.056	1.19	1.05 to 1.37	0.008

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

received cisatracurium having a greater baseline severity of disease, after statistical adjustment, we could find no difference in mortality between patients treated with cisatracurium compared with vecuronium in our primary analysis. If the mortality benefit of neuromuscular blockade observed in clinical trials derived from a class effect, these findings suggest that both drugs are equally efficacious at reducing mortality. However, cisatracurium demonstrated a consistent decrease in ventilator days and ICU days compared with vecuronium across multiple methods of analysis. These findings suggest that the nonpulmonary effects of cisatracurium—specifically its decreased association with ICU-associated weakness and faster metabolic clearance—may lead to decreased lengths of stay (10). This is additionally supported by the finding that hospital survivors treated with cisatracurium were more likely to be discharged to home in the linear regression model. Although the likelihood of discharge to home was not significantly different in the propensity-matched model, the magnitude of the difference between groups was consistent between the primary propensity analysis and the linear regression analysis, suggesting that the study may be underpowered to detect a difference after propensity matching.

Our study has several strengths. First, the Premier Incorporated Database included pharmacy data for a large number of critically ill patients. Although use of a large administrative database is associated with several limitations detailed below, the Premier Incorporated Database provides one of the few available options to answer these study questions. Recruiting patients into a large randomized control trial to answer these questions is likely impractical. Second, we implemented a variety of statistical methods—propensity matching, propensity modeling, and multivariate regression—all of which yielded consistent results. We controlled for differences between hospitals by including each hospital as a random effect in our final mixed-effects models. Third, cisatracurium was inherently used in patients with an

increased severity of disease. Patients treated with cisatracurium were older and had more severe disease as measured by evidence of multiorgan dysfunction (more septic shock, liver failure, renal failure, and encephalopathy). Despite this bias, we still demonstrated improved outcomes with cisatracurium.

Our study also has several limitations. First, multiple unmeasured confounding variables may exist. However, there are several reasons why indication bias does not explain these results. First, we limited our analysis to patients who received neuromuscular blockade within 48 hours of hospital admission to decrease the chance of significant changes in patient status from initial admission diagnosis. Second, patients treated with cisatracurium were older and had more evidence of multiorgan failure than did patients treated with vecuronium at baseline. These data should bias our findings in favor of vecuronium. Despite this, our analysis showed improved outcomes with cisatracurium. Third, clinically there is little reason to preferentially use vecuronium over cisatracurium in patients with multiorgan failure given its dependence on hepatic and renal function for clearance. Finally, we utilized propensity matching, regression modeling, and sensitivity analysis to control for a variety of patient and hospital confounders. However, indication bias remains a clear limitation and may still exist despite these precautions. Second, the Premier Database does not include laboratory results, imaging findings, or details of clinical decision making. Thus, we are unable to adjust for severity of illness scores such as APACHE (Acute Physiology and Chronic Health Evaluation) or SAPS (Simplified Acute Physiology Score) or severity of ARDS (as determined by the P/F ratio [the ratio of PaO_2 to the fraction of inspired oxygen]). This prevented an analysis of patients who were eligible for neuromuscular blockade but did not receive neuromuscular blockade. Third, diagnoses are determined using ICD-9-CM codes. Misclassification and underclassification are possible. Although misclassification is often assumed to be nondifferential and thus bias

results toward the null, this may not be a true assumption and we are unable to evaluate for systemic bias introduced by nondifferential or differential misclassification (28–30). Fourth, the patients' primary indication for mechanical ventilation is unknown. Ideally, we would study patients with severe hypoxemic respiratory failure. Like Papazian and colleagues (9), we included patients who received neuromuscular blockade within 48 hours of initiation of mechanical ventilation to avoid unmeasured confounding introduced by change in clinical status after hospital admission. Fifth, drug administration is based on hospital charges. Although we can determine whether a specific infusion was charged to the patient, we cannot determine how much of the infusion was administered to the patient. Sixth, because there was not a significance difference in mortality, total ventilator days—and not ventilator-free days—were used as an outcome variable to overcome the inherent difficulty of modeling a severely nonnormal outcome such as free days. Thus, it is possible that part of the reduction in ventilator days is associated with nonstatistically significant differences in mortality between groups. Seventh, propensity matching results in studying only a subset of the population, which may limit generalizability. Finally, this is an observational study and thus causal associations cannot be determined.

Conclusions

When compared with vecuronium, cisatracurium was associated with improved outcomes for patients at risk for and with ARDS. Therefore, cisatracurium may be the neuromuscular blockade agent of choice for these patients. Further research is needed to evaluate the mechanism underlying these differences, and to validate these findings in other cohorts of critically ill patients. ■

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