Treatment With Neuromuscular Blocking Agents and the Risk of In-Hospital Mortality Among Mechanically Ventilated Patients With Severe Sepsis*

Jay S. Steingrub, MD[1,2]; Tara Lagu, MD, MPH[2,3,4]; Michael B. Rothberg, MD, MPH[5]; Brian H. Nathanson, PhD[6]; Karthik Raghunathan, MD, MPH[7]; Peter K. Lindenauer, MD, MSc[2,3,4]

Objectives: Recent trials suggest that treatment with neuromuscular blocking agents may improve survival in patients requiring mechanical ventilation for acute respiratory distress syndrome. We examined the association between receipt of a neuromuscular blocking agent and in-hospital mortality among mechanically ventilated patients with severe sepsis.

Design: A pharmacoepidemiologic cohort study of patients with sepsis and a respiratory infection who had been admitted to intensive care and placed on mechanical ventilation within the first 2 days of hospitalization. We used propensity score matching and instrumental variable methods to compare the outcomes of patients treated with neuromuscular blocking agents within the first 2 hospital days to those who were not. Sensitivity analysis was used to model the effects of a hypothetical unmeasured confounder.

Setting: Three hundred thirty-nine U.S. hospitals that participated in the Premier Perspective database between 2004 and 2006.

Patients: Seven thousand eight hundred sixty-four patients met inclusion criteria, including 1,818 (23%) who were treated with a neuromuscular blocking agent by hospital day 2.

Interventions: None.

Measurements and Main Results: Patients who received neuromuscular blocking agents were younger (mean age, 62 vs 68), more likely to be treated with vasopressors (69% vs 65%) and had a lower in-hospital mortality rate (31.9% vs 38.3%, $p < 0.001$). In 3,518 patients matched on the propensity for treatment, receipt of a neuromuscular blocking agent was associated with a reduced risk of in-hospital mortality (risk ratio, 0.88; 95% CI, 0.80, 0.96). An analysis using the hospital neuromuscular blocking agent-prescribing rate as an instrumental variable found receipt of a neuromuscular blocking agent associated with a 4.3% (95% CI, −11.5%, 1.5%) reduction in in-hospital mortality.

Conclusions: Among mechanically ventilated patients with severe sepsis and respiratory infection, early treatment with a neuromuscular blocking agent is associated with lower in-hospital mortality. (*Crit Care Med* 2014; 42:90–96)

Key Words: mechanical ventilation; mortality; neuromuscular blocking agents; sepsis

***See also p. 208.**

[1]Division of Pulmonary and Critical Care Medicine, Baystate Medical Center, Springfield, MA.

[2]Department of Medicine, Tufts University School of Medicine, Boston, MA.

[3]Center for Quality of Care Research, Baystate Medical Center, Springfield, MA.

[4]Division of General Medicine, Baystate Medical Center, Springfield, MA.

[5]Department of Medicine, Medicine Institute, Cleveland Clinic, Cleveland, OH.

[6]OptiStatim, LLC, Longmeadow, MA.

[7]Department of Anesthesiology, Duke University Medical Center Anesthesiology Service, Durham VA Medical Center, Durham, NC.

Drs. Steingrub, Lagu, Rothberg, and Lindenauer were involved in the conception, hypothesis delineation, and design of the study. Drs. Steingrub, Lagu, Rothberg, Nathanson, Raghunathan, and Lindenauer were involved in the acquisition of the data or the analysis and interpretation of such information. Drs. Steingrub, Lagu, Rothberg, Nathanson, Raghunathan, and Lindenauer were involved in writing the article or substantially involved in its revision prior to submission.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Presented, in part, at the minisymposium, "Lung Injury in the Intensive Care Unit: Mechanisms, Therapies, Physiology, and Outcomes," 2011 ATS Annual Meeting, Denver, CO.

Dr. Steingrub received grant support from the National Heart, Lung, and Blood Institute (Acute Respiratory Distress Syndrome Network). Dr. Nathanson's company, OptiStatim, LLC, has a paid consulting agreement with Baystate Medical Center. Dr. Raghunathan received grant support for research from the Department of Anesthesiology, Duke University Medical Center. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Address requests for reprints to: Peter K. Lindenauer, MD, MSc, Center for Quality of Care Research, Baystate Medical Center, 759 Chestnut Street, Springfield, MA 01199. E-mail: peter.lindenauer@bhs.org

DOI: 10.1097/CCM.0b013e31829eb7c9

Despite limited evidence from clinical trials, neuromuscular blocking agents are widely used in the management of critically ill patients to facilitate intubation, mechanical ventilation, reduce oxygen consumption, lower intracranial pressure, and treat muscle spasms associated with tetanus. When used to facilitate mechanical ventilation, guidelines developed by the Society of Critical Care Medicine suggest that neuromuscular blocking agents should be reserved for those instances in which desired levels of ventilator synchrony have not been achieved despite optimal use of sedative and analgesic medications, since the potential benefit of these medications must be weighed against the risk of ICU-acquired weakness (ICUAW) (1–5).

In the specific setting of the acute respiratory distress syndrome (ARDS), small randomized trials have found that a brief period of paralysis within the first 48 hours of the onset of ARDS may reduce inflammation, improve oxygenation, and increase survival (6, 7). Several mechanisms have been hypothesized to explain these benefits, including a direct anti-inflammatory effect, improved respiratory compliance, and the prevention of spontaneous respiratory movements responsible for dyssynchrony and worsening gas exchange, which may facilitate the optimization of lung-protective ventilation strategy for patients (8–10). It has been estimated that neuromuscular blocking agents are now used in as many as 45% of cases of ARDS (11).

However, among the general population of patients with severe sepsis requiring mechanical ventilation, the risks and benefits of neuromuscular blockade are less well understood. We therefore examined the association between receipt of a neuromuscular blocking agent and in-hospital mortality among a large cohort of patients with severe sepsis and a respiratory source of infection who were treated with mechanical ventilation.

MATERIALS AND METHODS

Setting and Subjects

We conducted a retrospective cohort study of patients admitted between June 1, 2004, and June 30, 2006, to a geographically and structurally diverse set of hospitals participating in Perspective (Premier Healthcare Informatics, Charlotte, NC), a voluntary, fee-supported database for measuring quality and resource utilization. In addition to information available in standard hospital discharge files, the Perspective database contains an itemized, date-stamped log of all charges, including medications, laboratory tests, and diagnostic and therapeutic services provided to each patient.

Patients were included in our analysis if they were more than or equal to 18 years old, had a principal or secondary diagnosis of sepsis as defined by Martin et al (12) (*International Classification of Diseases*, 9th Edition, Clinical Modification [ICD-9-CM] codes: 038, 020.0, 790.7, 117.9, 112.5, 112.81, as well as 995.92), were admitted to an ICU, placed on a ventilator, underwent blood culture, and were treated with antibiotics all within the first 2 hospital days. The study was limited to patients with severe sepsis, evidenced by respiratory failure, early in the hospitalization so that we could control for patient differences using information available at admission. Additionally, we limited the study to medical patients with a respiratory source of sepsis because pneumonia is a common source of ARDS. Because the study focus was exposure to neuromuscular blocking agents during the first 2 hospital days, patients who died during this time period were excluded to eliminate the threat of immortal time bias (13). We also excluded patients transferred from or to another acute care facility because we could not determine the onset or subsequent course of their illness. Permission to conduct the study was obtained from the institutional review board at Baystate Medical Center.

Patient and Hospital Information

In addition to patient age, gender, race, ethnicity, marital status, and primary insurance coverage, we recorded the presence of up to 29 comorbidities using software provided by the Healthcare Costs and Utilization Project of the Agency for Healthcare Research and Quality. Using diagnosis codes we assessed the type of infection (gram positive, gram negative, mixed, anaerobic, and fungal). We recorded key characteristics (number of beds, teaching status, and geographic region) for each hospital that participated.

Use of Neuromuscular Blocking Agents and Other Treatments

We reviewed each patient's pharmacy charge file to determine whether neuromuscular blocking agents (atracurium, cisatracurium, doxacurium, mivacurium, pancuronium, rocuronium, or vecuronium) were administered on at least 1 day during the first 2 days of hospitalization. Because its use is generally limited to induction, succinylcholine was not considered to be a neuromuscular blocking agent for the purposes of the study; however, we adjusted for exposure to succinylcholine in the multivariate analysis. Patients who received neuromuscular blocking agents beginning on day 3 or later were categorized in the untreated group because late treatment can be a marker for clinical deterioration.

To control for differences in severity of illness and the effects of other therapies, we assessed the use of a wide range of diagnostic tests, monitoring devices, and pharmacologic treatments administered within the first 2 days (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A712).

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included the number of days on mechanical ventilation, the number of ventilator-free days within the first 28 days, and the lengths of stay in the ICU and hospital. We also examined secondary diagnosis codes to assess the development of ICUAW based on ICD-9-CM codes, and barotrauma, as evidenced by insertion of a chest tube after hospital day 2, or a diagnosis code of pneumothorax.

Analysis

We calculated summary statistics using frequencies and proportions for categorical data, and means, medians, and interquartile ranges for continuous variables. We compared the characteristics of patients who received a neuromuscular blocking agent during the first 2 hospital days with those who did not using chi-square or *z*-tests.

We developed a nonparsimonious logistic regression model to estimate a patient's propensity for treatment that included all patient and hospital characteristics and all other early treatments and diagnostic tests (**Supplemental Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A712) in which receipt of a neuromuscular blocking agent by day 2 was considered the outcome. Each patient who was treated with a neuromuscular blocking agent was then matched with a nontreated patient with a similar treatment propensity using a Greedy Match algorithm (14). The matched cohort was evaluated for differences on each covariate (a balance assessment) to ensure that there was no statistical difference in the covariates between groups (15).

We compared the mortality and secondary outcomes between treated and untreated patients in this matched cohort and performed stratified analyses to assess for heterogeneity in the association between neuromuscular blocking agent treatment and mortality across age categories, the number of organ supportive therapies, and receipt of vasopressors. The paired nature of the data (e.g., a paired *t* test) was taken into account.

In a sensitivity analysis, we restricted the sample to patients who received at least two consecutive days of neuromuscular blocking agent treatment, or who on a single day, received a dose suggestive of continuous infusion (> 100 mg atracurium, 40 mg cisatracurium, 20 mg pancuronium, 100 mg rocuronium, or 20 mg vecuronium). As a second sensitivity analysis, we explored how the presence of a hypothetical unmeasured confounder might influence the effect estimate of neuromuscular blocking agent therapy. Given the range of values we observed among the known confounders in our study, we estimated that an influential *unmeasured* confounder would increase the risk of mortality by 1.25–1.75 times and might be present in as many as 40% of untreated patients but absent in those treated with neuromuscular blocking agents. We then quantified the effect of such an unmeasured confounder under these scenarios based on the methods described by Lin et al (16).

Lastly, to address concerns about residual unmeasured confounding, we performed an instrumental variable analysis using the hospital neuromuscular blocking agent treatment rate as the instrument. We observed that use of neuromuscular blocking agents varied substantially across hospitals (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A712) and that hospital treatment rates were largely independent of patient characteristics (**Supplemental Table 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/A712), suggesting that this could serve as an effective instrumental variable. We created two bivariate probit models for mortality (since the outcome was binary) in which patients were assigned their respective hospital's neuromuscular blocking agents-prescribing rate in place of their actual treatment. The first model only used the neuromuscular blocking agent instrumental variable as a predictor and the second used this instrumental variable and all other predictors in the propensity score model (but not the propensity score). CIs were derived via bootstrapping on 500 iterations with replacement (17).

Statistical analyses were carried out using Stata/SE 10.0 (StataCorp, College Station, TX).

RESULTS

Among the 7,864 patients who met our enrollment criteria (**Fig. 1**), the mean age was 66 years, 55% were male, 63% were white, and 2,892 patients (36.8%) died during the hospitalization (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A712). When compared with those who did not receive early neuromuscular blocking agent therapy, 1,818 patients (23%) treated with neuromuscular blocking agents within the first 2 hospital days were younger (62 vs 68 yr), more likely to be male (59% vs 54%), to receive vasopressors (69% vs 65%), and to require other organ supportive therapies, including bicarbonate administration, dialysis, and fresh frozen plasma or platelets. Treated patients received therapy for a mean of 1.5 days and had a mean length of stay of 13.5 days as compared to 14.1 days for untreated patients. Both groups spent a mean of 7.7 days on mechanical ventilation. The unadjusted in-hospital mortality rate of patients initially treated with neuromuscular blocking agents was 31.9% versus 38.3% among those who did not receive therapy.

Results of Propensity-Matched Analyses

Overall, 97% of patients treated with a neuromuscular blocking agent by hospital day 2 were successfully matched to a nontreated patient with a similar propensity, achieving full covariate balance (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A712). Within this sample, the in-hospital mortality rate was 31.7% among treated patients and 36.1% in the matched controls (risk ratio of inhospital mortality, 0.88; 95% CI, 0.80–0.96) (**Table 1**) Hospital and ICU lengths of stay were 13.5 and 8.8 days in the treated group and 13.8 and 8.9 in the untreated. Both groups spent 7.7 days on mechanical ventilation and both had 20.5 ventilator-free days. ICUAW was documented in only five patients (0.28%) in the neuromuscular blocking agent-treated group and three patients (0.17%) in the untreated group ($p = 0.48$). Fewer patients who were treated with a neuromuscular blocking agent had a chest tube inserted after the second hospital day; however, the combined prevalence of a diagnosis code for pneumothorax or chest tube insertion was similar in the two groups. Readmission rates were similar.

In analyses stratified by the receipt of additional organ supportive therapies, receipt of vasopressors, and age, treated patients had lower mortality in all strata. Although the difference was not statistically significant for subgroups,

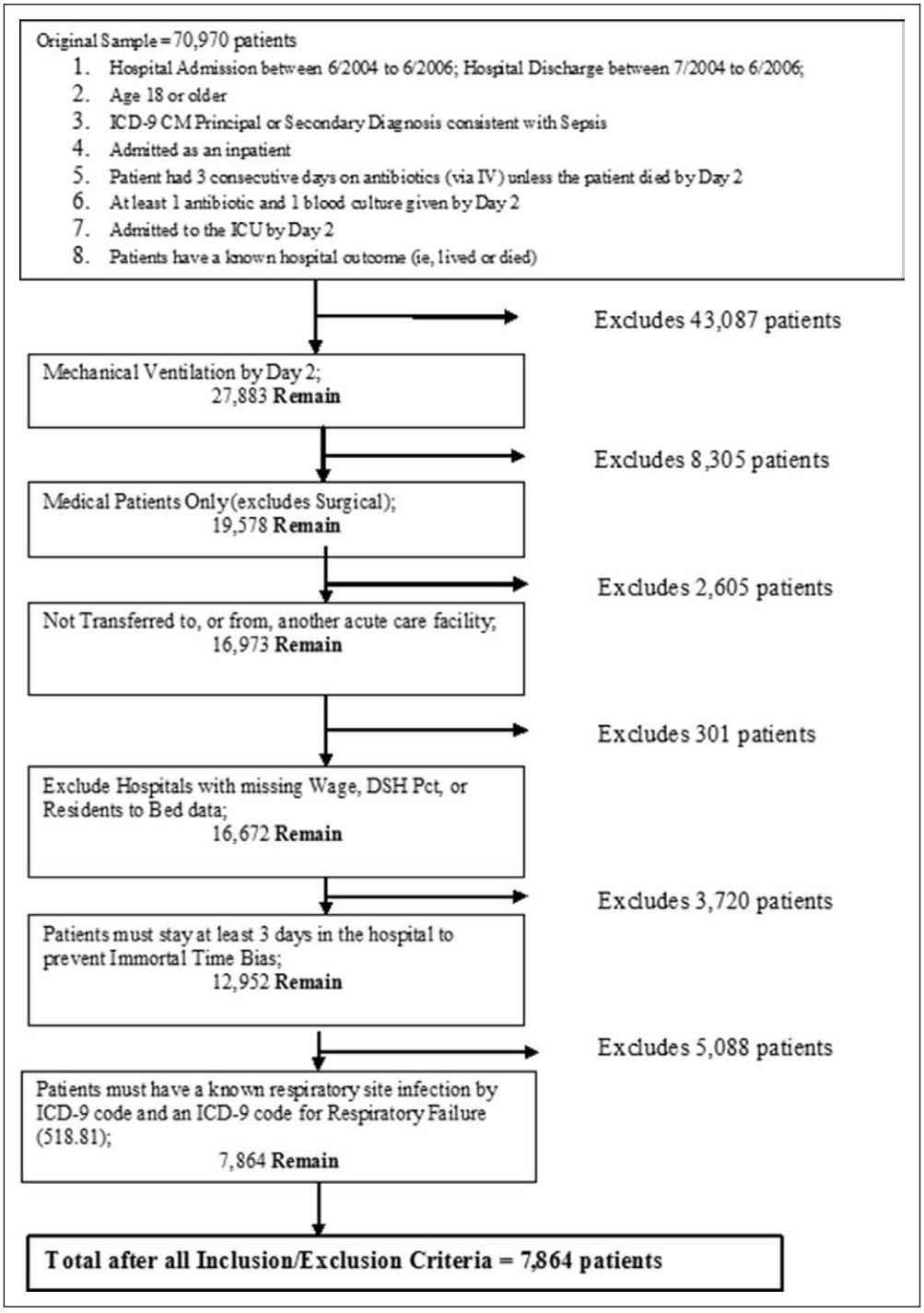

Figure 1. Development of study cohort. ICD-9 CM = *International Classification of Diseases*, 9th Edition, Clinical Modification, DSH Pct = disproportionate share hospital percentage.

neuromuscular blocking agent-treated patients retained a mortality benefit in every subgroup (**Fig. 2**).

In a sensitivity analysis restricted to patients who received two consecutive days of neuromuscular blocking agents, or who exceeded a daily threshold consistent with continuous infusions dosing, the effect estimate suggested increased risk of mortality associated with neuromuscular blocking agent treatment, but the results were nonsignificant (relative risk, 1.10; 95% CI, 0.91–1.33; $p = 0.33$). In an additional sensitivity analysis, an unmeasured confounder that was associated with a 50% increased risk of mortality and that was absent in the treated patients would need to be present in 10% of the untreated patients to render the association we observed nonsignificant (**Table 2**).

Results of Instrumental Variable Analyses

Across the 339 hospitals that contributed greater than or equal to 30 study patients, the proportion of patients receiving neuromuscular blocking agents by day 2 ranged from 0% to greater than 60% (Supplemental Fig. 1 and Supplemental Table 3, Supplemental Digital Content 1, http://links.lww.com/CCM/A712). We categorized hospitals into quintiles (Q) according to their rate of use (Q1–Q5, 2.2%, 11.1%, 20.7%, 32%, and 49%). In the instrumental variable model adjusted for all confounders, the estimated reduction in mortality associated with receipt of neuromuscular blocking agent therapy was 4.3% (95% CI, –11.5%, 1.5%), similar to the 4.4% reduction derived from the propensity-matched analysis (Table 1).

DISCUSSION

In this large observational study, we found that among mechanically ventilated patients with severe sepsis and a respiratory source of infection, those prescribed a neuromuscular blocking agent early in the hospital course were less likely to die in hospital than similar patients who did not receive treatment or in whom treatment commenced later. These findings were robust to sensitivity analysis and alternative approaches to effect estimation, including instrumental variable methods.

In the face of limited evidence concerning the benefits of neuromuscular blocking agent therapy, surveys have reported substantial variation in their use by critical care physicians (2, 18, 19). In the treatment of patients with ARDS, there has been growing

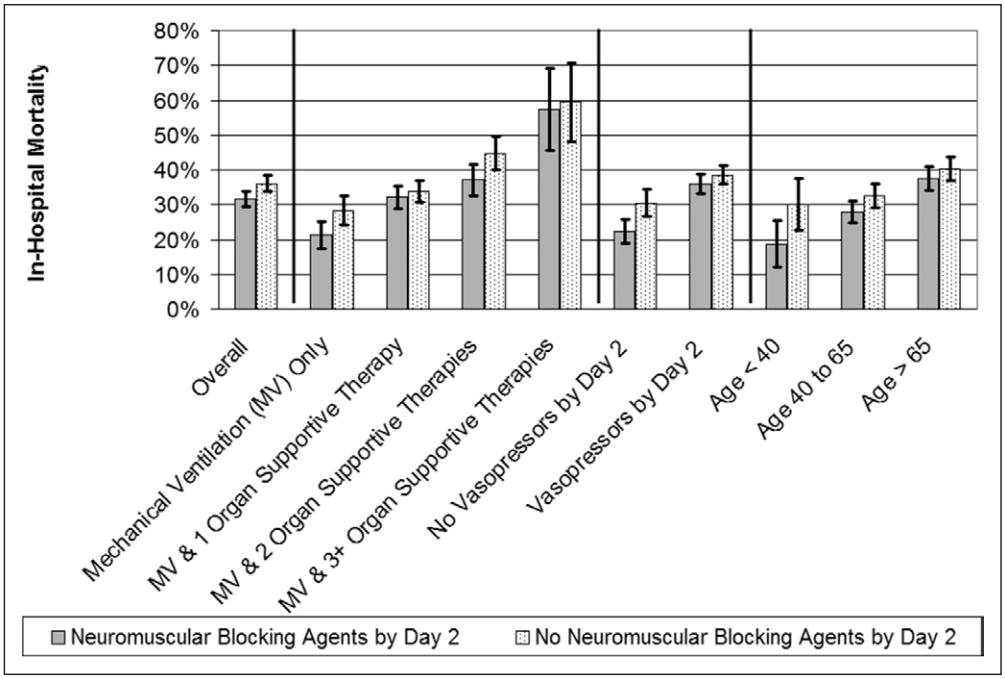

Figure 2. Mortality among patients treated or not treated with neuromuscular blocking agents in the propensity-matched cohort, stratified by the number of organ supportive therapies, receipt of vasopressors, and age. MV = mechanical ventilation.

interest in the role that a brief period of paralysis might play in reducing the risk of ventilator-associated lung injury. A study of 36 patients found reduced levels of inflammatory biomarkers and improved oxygenation among patients receiving low tidal volume ventilation who were administered cisatracurium as compared to patients receiving low tidal volume ventilation alone (6). Additionally, in the ARDS et Curarisation Systematique (ACURASYS), a multicenter randomized controlled trial that enrolled 340 patients with severe ARDS, early administration of cisatracurium combined with a low tidal volume ventilation strategy was associated with a reduced risk of barotrauma, more ventilator-free and organ failure-free days, and a 29% mortality reduction, without increased muscle weakness (7).

In contrast to ACURASYS, our analysis included patients with sepsis and a respiratory source of infection who were treated with mechanical ventilation at the time of hospital admission. Although it is likely that some of these patients had acute lung injury or ARDS, mortality among the untreated patients in the propensity-matched sample was lower than in the untreated patients in ACURASYS, suggesting a lower average level of severity. Further, the risk ratio estimate for inpatient mortality associated with neuromuscular blocking agent therapy in this study (0.88) suggests less benefit from neuromuscular blockade than the 0.78 relative risk reported by the ACURASYS investigators. There are several possible explanations for this discrepancy, including differences in the populations studied, in the dosing and administration of neuromuscular blocking agent therapy, and in the delivery of mechanical ventilation.

In the International Study of Mechanical Ventilation (IMV), Arroliga et al (1) observed that neuromuscular blocking agents were prescribed to 13% of patients for a median duration of 2 days. Receipt of neuromuscular blocking agent therapy was associated with higher mortality in both univariate and multivariate analyses, leading the authors to speculate that neuromuscular blockers appear to be a "final option in the management of severely ill patients." Although these findings contrast with ours, the IMV was not limited to medical patients with respiratory infection.

Because this was an observational study and treatment assignment was not random, there is a risk that residual selection bias could be responsible for the observed association between receipt of neuromuscular blocking agents and improved survival. This would be the case if neuromuscular blocking agents were preferentially prescribed to those patients with a higher pretreatment likelihood of survival. We undertook several strategies to minimize these threats and to test the robustness of our effect estimates. First, we adjusted for a large number of potential confounders, including patient demographics, other medical therapies such as sedatives and analgesics, and important hospital characteristics, using standard regression methods as well as propensity matching and stratification. Since these techniques do not directly control for the effects of unmeasured confounders, we carried out an instrumental variable analysis using the hospital rate of neuromuscular blocking agent use as the instrument, a common econometric technique increasingly used in comparative effectiveness research (20–23). We are more confident that the beneficial effect estimates observed in the primary analysis are robust since the effect estimates obtained using instrumental variable methods were similar to those derived from the propensity and regression analyses. Despite these reassurances, our observation of reduced mortality associated with receipt of neuromuscular blocking agent therapy was relatively sensitive to the effects of residual confounding.

A second limitation is that the study is based on highly detailed billing data, not chart review. However, ICD-9-CM codes are an acceptable method of identifying patients with sepsis, and we strengthened our findings by strict inclusion and exclusion criteria that took into account additional clinical information. At the same time, if greater heterogeneity of the patients we studied meant that some groups experienced benefit while other did not, then extrapolating the benefits of neuromuscular blocking agent therapy to all mechanically ventilated

TABLE 1. Results of Propensity-Matched and Instrumental Variable Analyses

Outcome	Overall *n* = 3,518 *n* (%)	Treated *n* = 1,759 *n* (%)	Untreated *n* = 1,759 *n* (%)	*p*
Mortality	1,192 (33.9)	635 (36.1)	557 (31.7)	0.006
Hospital LOS	13.6 (9.7)	13.8 (9.7)	13.5 (9.8)	0.05
ICU LOS	8.9 (5.9)	8.9 (5.9)	8.8 (5.8)	0.45
Ventilator-free days	21.1 (4.7)	21.1 (4.6)	21.1 (4.8)	0.84

Method	Absolute Difference[a]	Lower 95% CI	Upper 95% CI
Unadjusted	−6.4%	−8.9%	−3.9%
Instrumental variable bivariate probit model—percentile-based CIs, 500 bootstraps but not adjusted for other confounders	−7.5%	−13.7%	−1.9%
Instrumental variable bivariate probit model—percentile-based CIs, 500 bootstraps, all other variables in the model	−4.3%	−11.5%	1.5%
Propensity score method for comparison	−4.4%	−7.6%	−1.3%

LOS = length of stay.

[a]Lower values reflect a benefit for neuromuscular blocking agents.

patients with respiratory infection could lead to overtreatment. Similarly, while we did not have direct physiologic measurements, the rich dataset allowed us to adjust for the receipt of organ supportive therapies, including vasopressors and dialysis that were useful proxies for severity. To this end, the discrimination of the mortality model we created was similar to Acute

TABLE 2. Sensitivity Analysis to Quantify the Effects of a Hypothetical Unmeasured Confounder on Study Results

Increase in the Risk of Hospital Mortality Due to the Confounder	Prevalence of the Confounder Among Untreated Patients When It Is Absent in the Treated Patients (%)	Relative Risk (95% CI)
Baseline	0	0.88 (0.80–0.96)
1.25	5	0.89 (0.81–0.97)
1.25	10	0.90 (0.82–0.99)
1.25	20	0.92 (0.84–1.01)[a]
1.25	30	0.94 (0.86–1.03)[a]
1.25	40	0.97 (0.88–1.06)[a]
1.50	5	0.90 (0.82–0.99)
1.50	10	0.92 (0.84–1.01)[a]
1.50	20	0.97 (0.88–1.06)[a]
1.50	30	1.01 (0.92–1.11)[a]
1.50	40	1.05 (0.96–1.15)[a]
1.75	5	0.91 (0.83–1.00)
1.75	10	0.94 (0.86–1.03)[a]
1.75	20	1.01 (0.92–1.11)[a]
1.75	30	1.07 (0.98–1.18)[a]
1.75	40	1.14 (1.04–1.25)[b]

[a]Not significant.

[b]Significant and changed direction.

Physiology and Chronic Health Evaluation II for patients with sepsis (24). Also, we note that ICUAW was only assessed via ICD-9-CM code and the low prevalence is likely due to undercoding this condition. Another limitation is that we did not have information about mechanical ventilator practices and settings, and it is unlikely that many patients received lung-protective ventilation delivered by strict protocol. If the benefit of neuromuscular blocking agent therapy depends on the codelivery of low tidal volume ventilation, then our results may underestimate the true benefit of therapy. Similarly, we did not have information about the circumstances or factors that led physicians to prescribe neuromuscular blocking agents. Although we adjusted for differences in the use of sedatives and other analgesic agents among the treated and untreated patients, we had limited information about medication dosing or specific treatment protocols. Fourth, our dataset did not allow us to measure duration of therapy with any greater resolution than the number of unique calendar days. The majority of the patients enrolled in this study received only 1 day of treatment, and it is possible that in many cases the intention was to facilitate intubation, not to facilitate mechanical ventilation synchrony. In this regard, a sensitivity analysis restricted to patients who received 2 or more days of therapy, or daily doses indicative of infusion, did not show a benefit associated with treatment. A final limitation is that we did not have access to long-term outcomes.

CONCLUSIONS

Among critically ill patients with severe sepsis and a respiratory source of infection treated with mechanical ventilation, receipt of neuromuscular blocking agent is associated with improved inpatient survival. Given the enormous clinical and economic impact of sepsis, randomized trials are needed to confirm these benefits.

ACKNOWLEDGMENTS

We thank Nicholas Hannon for his assistance with article preparation.

REFERENCES

1. Arroliga A, Frutos-Vivar F, Hall J, et al; International Mechanical Ventilation Study Group: Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. *Chest* 2005; 128:496–506
2. Mehta S, Burry L, Fischer S, et al; Canadian Critical Care Trials Group: Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. *Crit Care Med* 2006; 34:374–380
3. Murray MJ, Cowen J, DeBlock H, et al; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists, American College of Chest Physicians: Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med* 2002; 30:142–156
4. Latronico N, Fenzi F, Recupero D, et al: Critical illness myopathy and neuropathy. *Lancet* 1996; 347:1579–1582
5. De Jonghe B, Sharshar T, Lefaucheur JP, et al; Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation: Paresis acquired in the intensive care unit: A prospective multicenter study. *JAMA* 2002; 288:2859–2867
6. Forel JM, Roch A, Marin V, et al: Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. *Crit Care Med* 2006; 34:2749–2757
7. Papazian L, Forel JM, Gacouin A, et al; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107–1116
8. Slutsky AS: Neuromuscular blocking agents in ARDS. *N Engl J Med* 2010; 363:1176–1180
9. Kondili E, Prinianakis G, Georgopoulos D: Patient-ventilator interaction. *Br J Anaesth* 2003; 91:106–119
10. Tobin MJ, Jubran A, Laghi F: Patient-ventilator interaction. *Am J Respir Crit Care Med* 2001; 163:1059–1063
11. Forel JM, Roch A, Papazian L: Paralytics in critical care: Not always the bad guy. *Curr Opin Crit Care* 2009; 15:59–66
12. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
13. Suissa S: Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008; 167:492–499
14. Kurth T, Walker AM, Glynn RJ, et al: Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol* 2006; 163:262–270
15. Austin PC, Grootendorst P, Anderson GM: A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: A Monte Carlo study. *Stat Med* 2007; 26:734–753
16. Lin DY, Psaty BM, Kronmal RA: Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* 1998; 54:948–963
17. Chiburis RC, Das J, Lokshin M: A Practical Comparison of the Bivariate Probit and Linear IV Estimators. World Bank Policy Research Working Paper No. 5601 [Internet]. March 1, 2011. Available at: http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1792259. Accessed June 15, 2011
18. Rhoney DH, Murry KR: National survey on the use of sedatives and neuromuscular blocking agents in the pediatric intensive care unit. *Pediatr Crit Care Med* 2002; 3:129–133
19. Samuelson KA, Larsson S, Lundberg D, et al: Intensive care sedation of mechanically ventilated patients: A national Swedish survey. *Intensive Crit Care Nurs* 2003; 19:350–362
20. McClellan M, McNeil BJ, Newhouse JP: Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. *JAMA* 1994; 272:859–866
21. Wang PS, Schneeweiss S, Avorn J, et al: Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005; 353:2335–2341
22. Stukel TA, Fisher ES, Wennberg DE, et al: Analysis of observational studies in the presence of treatment selection bias: Effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA* 2007; 297:278–285
23. Brookhart MA, Rassen JA, Schneeweiss S: Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010; 19:537–554
24. Lagu T, Lindenauer PK, Rothberg MB, et al: Development and validation of a model that uses enhanced administrative data to predict mortality in patients with sepsis. *Crit Care Med* 2011; 39:2425–2430