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The Implementation of Protocol-Based Utilization of Neuromuscular Blocking Agent Using Clinical Variables in Acute Respiratory Distress Syndrome Patients

OBJECTIVES: The recent conflicting data on the mortality benefit of neuromuscular blocking agents in acute respiratory distress syndrome and the potential adverse effects of continuous neuromuscular blocking agent necessitates that these medications should be used judiciously with dose reduction in mind. The aims of the study were to improve the process of care by provider education of neuromuscular blocking agent titration and monitoring and to determine the impact of clinical endpoint based neuromuscular blocking agent titration protocol.

DESIGN: We conducted a proof-of-concept historically controlled study of protocol-based intervention standardizing paralytic monitoring and titration using clinical variables. Education of the protocol was provided to ICU staff via bedside teaching and workshops. The primary outcomes were the time to reach goal paralysis and cumulative neuromuscular blocking agent dose. Secondary outcomes included maintenance of deeper sedation (Richmond Agitation and Sedation Scale -5) prior to neuromuscular blocking agent initiation, total time on mechanical ventilation, length of stay, and mortality.

SETTING: Medical ICU at a quaternary academic hospital between March 2019 and June 2020.

PATIENTS: Adult severe acute respiratory distress syndrome ($PaO_2/FiO_2 < 150$) patients requiring neuromuscular blocking agent for greater than or equal to 12 hours. Eighty-two patients fulfilled inclusion criteria, 46 in the control group and 36 in the intervention group.

INTERVENTIONS: Education and implementation of standardized protocol.

MEASUREMENTS AND MAIN RESULTS: Compared with the control group, the time to reach goal paralysis in the intervention group was shorter (8.55 ± 9.4 vs 2.63 ± 5.9 hr; $p < 0.0001$) on significantly lower dose of cisatracurium (total dose $1,897.96 \pm 1,241.0$ vs 562.72 ± 546.7 mg; $p < 0.0001$ and the rate 5.84 ± 2.66 vs 1.99 ± 0.95 $\mu\text{g}/\text{kg}/\text{min}$; $p < 0.0001$). Deeper sedation was achieved at the time of initiation of neuromuscular blocking agent in the intervention arm (mean Richmond Agitation and Sedation Scale -3.3 ± 1.9 vs -4.3 ± 1.7 ; $p = 0.015$). There was no significant difference in total time on mechanical ventilation, length of ICU stay, length of hospital stay, and mortality between the two groups.

CONCLUSIONS: Implementation of comprehensive education, standardization of sedation prior to neuromuscular blocking agent initiation, integration of clinical variables in determining paralysis achievement, and proper

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DOI: 10.1097/CCE.0000000000000371

use of peripheral nerve stimulation served as optimal strategies for the titration and monitoring of neuromuscular blocking agent in acute respiratory distress syndrome. This reduced drug utilization while continuing to achieve benefit without causing adverse effects.

KEY WORDS: acute respiratory distress syndrome; intensive care unit; neuromuscular blocking agents; sedation; train-of-four monitoring

Severe acute respiratory distress syndrome (ARDS) is a life-threatening condition with significant morbidity and overall mortality often exceeding 40% (1). A few interventions have shown to improve outcomes, including lung-protective ventilation strategy, prone positioning, and early use of continuous neuromuscular blocking agent (NMBA) in moderate to severe ARDS (P_{aO_2}/F_{iO_2} ratio < 150) (2–4). Commonly cited reasons for use of NMBAs in ARDS include reduction of patient-ventilator dyssynchrony and work of breathing, along with facilitation of mechanical ventilation to allow high positive end-expiratory pressure and prone positioning (5).

Although the results of three recent meta-analyses demonstrated that early continuous paralytic administration in patients with ARDS was associated with reduced barotrauma and improved oxygenation, its impact on mortality remains unclear (6–8). Of two notable prospective trials studying continuous paralytic infusion in this population, the first showed lower mortality, whereas the second more recent trial showed no benefit (9). Furthermore, prolonged infusion of NMBA is associated with the detrimental side effect of subsequent neuromuscular weakness that can be both profound and irreversible. Clinical practice guidelines for sustained NMBA use in critically ill patients recommends a short course (i.e., 48 hr) of paralysis for severe ARDS patients. Surviving Sepsis Campaign endorsed similar recommendations in 2017 (10). However, there is lack of standardization regarding the titration of dose and monitoring of NMBAs (11). Despite acknowledging the limitations of train-of-four (TOF) monitoring, the Society of Critical Care Medicine and American Society of Health-System Pharmacists recommend the use of TOF in conjunction with the clinical variables (12). Therefore, further studies are required to establish a standardized, multimodal strategy for dose titration and monitoring to reduce the inconsistencies associated with any single modality.

The aims of this historically controlled single-center study were to improve the process of care by comprehensive provider education of NMBA titration and monitoring and to determine the impact of integrating clinical variables to NMBA titration protocol in severe ARDS patients.

METHODS

Design and Protocol

We conducted a proof-of-concept historically controlled study of protocol-based intervention targeting standardization of continuous paralytic usage via clinical endpoints in ARDS patients at an academic, quaternary medical center. We obtained institutional review board approval (protocol number 1904535385). Electronic medical records (EMRs) of West Virginia University hospital health system (WVUH) were reviewed to identify historic controls of adult severe ARDS (P_{aO_2}/F_{iO_2} < 150) patients admitted consecutively to medical ICU (March to September 2019) and requiring NMBA (cisatracurium) for greater than or equal to 12 hours. For these controls, cisatracurium usage was titrated solely on TOF nerve stimulation monitoring, whereas sedatives were monitored and titrated using bispectral index (BIS). The goal TOF was left up to the prescribing provider and could range from 1 to 3 (two most typically selected), and the BIS goal ranged from 40 to 60.

An electronic survey for healthcare providers was conducted to test knowledge and practices related to NMBA titration and monitoring. Thirty surveys were completed. After determining the knowledge gap, a multidisciplinary team of ICU physicians, pharmacists, and nurses drafted an evidence-based protocol focusing on clinical variables for NMBA administration and titration. It was implemented institution wide through the EMR. Comprehensive daily bedside teaching and weekly hands-on workshops were done for 2 months to teach the proper technique of TOF measurement and appropriate titration and monitoring of NMBA using clinical variables as per the protocol.

The protocol consisted three major changes: standardization of sedation prior to the initiation of neuromuscular blockade, integration of clinical goals in determining paralysis achievement, and use of peripheral nerve stimulation (PNS) to finely adjust paralytic dosing.

First, we established specific mandatory sedative goals defined as Richmond Agitation and Sedation

Scale (RASS) of -5 and BIS of less than 60 prior to initiating continuous paralytics (full protocol can be found as **Appendix 1**, <http://links.lww.com/CCX/A551>). This would ensure that patients were deeply sedated prior to the initiation of continuous NMBA. Once the sedation goals were achieved, sedatives and analgesics were not titrated throughout the duration of continuous NMBA use.

We then outlined a new goal of paralysis in severe ARDS patients primarily consisting of clinical variables rather than neuromuscular monitoring alone. Clinical variables of goal paralysis were defined as lack of cough or gag reflexes as well as lack of intrinsic respiratory drive (spontaneous breathing over the set ventilatory rate). TOF monitoring was standardized during the entire course of NMBA use. TOF was performed either on ulnar or posterior tibial nerves (**Fig. 1**) using the standard PNS device. The voltage, which generated the nerve stimulation response, was kept constant. Integration of physiologic variables and TOF were used to determine the titration of cisatracurium (**Table 1**). After the implementation of the protocol, a second phase of data collection was conducted (January to June 2020). Several steps were taken to ensure compliance to the protocol. As per policy, the nurses were required to document goal RASS and BIS in EMR prior to initiation of NMBA unless an exception was approved by treating physician. Medical ICU pharmacist verification of achievement of sedation goals was required prior to NMBA dosing. As per the institution policy, a physician performed all NMBA bolus administration. Nursing staff managed the infusion of NMBA, and a second nursing staff verification

was mandated for titration of NMBA once clinical variables were reached. Baseline TOF was done and documented after sedation goals were achieved. The same TOF device was used for all TOF assessment at the same voltage used for the baseline assessment. The nurses were required to document all of the above steps in the EMR every time neuromuscular blocking agent was administered. We used nursing documentation in EMR to determine the compliance with our NMBA protocol in the interventional arm.

The standard of care for both groups included lung-protective ventilation strategies using a low tidal volume of 6–8 mL/kg of predicted body weight. Prone positioning is often used in our ICUs for the treatment of ARDS, but the decision to prone patients was left to the discretion of the treating physician. Cisatracurium was the single NMBA used for paralysis in ARDS patients, and the intensivists determined the duration of therapy although they were prompted by nursing staff for the trial of cessation at 48 hours in the intervention group.

Primary outcomes of the study were the time to reach goal paralysis and cumulative NMBA dose. Secondary outcomes included maintenance of deeper sedation (RASS -5) before starting NMBA, total time on mechanical ventilation, length of ICU stay, length of hospital stay, and mortality.

Population and Data Collection

Inclusion criteria consisted of adult (> 18 yr old) patients admitted to the medical ICU with severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$) requiring paralytic usage for greater than or equal to 12 hours. We excluded patients if paralytics were used for any indication other than ARDS, total duration of NMBA use less than 12 hours, and pregnant females.

Baseline demographics, comorbid conditions, Acute Physiology and Chronic Health Evaluation (APACHE) IV within 24 hours of study inclusion, initial $\text{PaO}_2/\text{FiO}_2$ ratio, and time of initiation of paralytics were recorded. Outcome measures of time to achieve the goal paralysis, average rate and total amount of cisatracurium, RASS prior to initiation of paralysis, length of mechanical ventilation, length of hospital stay, and ICU stay were collected. Data

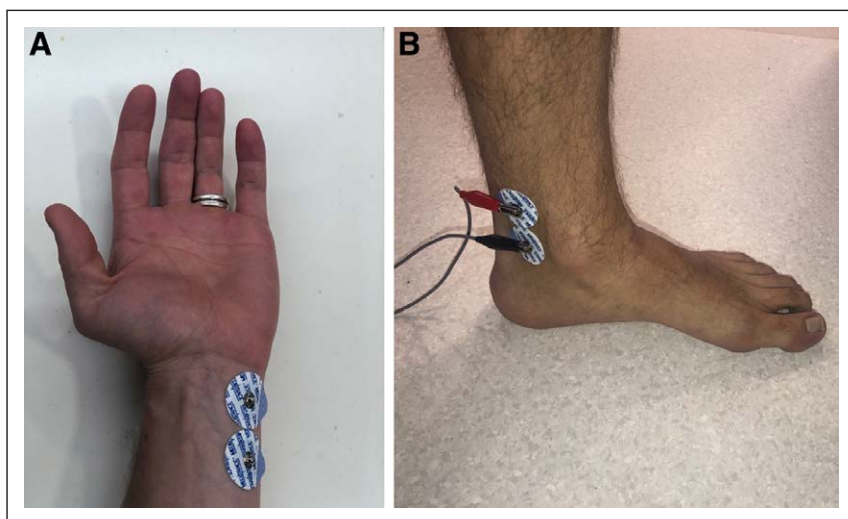


Figure 1. Peripheral nerve stimulation technique for ulnar (**A**) and posterior tibial nerve (**B**) showing location of proximal (red) and distal (black) electrodes.

TABLE 1.
Titration Chart of the Neuromuscular Blocking Agent Protocol Based on Clinical Variables

Clinical Endpoint/ Goal ^b Achieved	Train of Four	Recommended Paralytic Titration
Yes	1–4/4	Continue current dose
No	1–4/4	Increase paralytic dose by 0.5 µg/kg/min
Yes	0/4	Troubleshoot ^a and decrease paralytic dose by 0.5 µg/kg/min
No	0/4	Troubleshoot ^a and increase paralytic dose by 0.5 µg/kg/min

^aCheck placement of train of four (TOF), ensure paralytic is running correctly, try alternate TOF monitoring device.

^bGoal: Titrate paralytic infusion to meet the following clinical variables: patient is not spontaneously breathing over the vent, patient does not have a cough with suctioning, and patient does not have a gag reflex.

Recommend initial infusion rates of: Cisatracurium 2 µg/kg/min.

were aggregated using the HIPPA compliant Research Electronic Data Capture electronic data capture tools hosted at West Virginia Clinical and Translational Science Institute (13, 14). Net cost per vial of cisatracurium to the hospital pharmacy was used to complete all the cost calculations.

Statistical Analysis

SAS Version 9.4 (https://www.sas.com/en_us/company-information.html) was used for all statistical analysis. Mean and SDs were calculated for continuous variables, and proportions were calculated for categorical variables. Differences in outcomes by groups were presented as Welch's *t* tests for continuous variables, and chi-square *p* values for categorical variables. We used the Kaplan-Meier method to analyze "time-to-goal paralysis" and compared statistically using the log-rank test to test the null hypothesis of no difference in the probability of an event (time-to-goal paralysis) at any time point between the two groups ($\alpha = 0.05$). The magnitude of the difference between groups was quantified using Cox proportional hazard regression model and presented as the hazard ratio (HR). An alpha value of 0.05 was used as the cut off for all statistical tests.

RESULTS

Neuromuscular Blockade, Sedation, and Other Care Processes

Eighty-two patients fulfilled criteria for inclusion, 46 in the control group (pre protocol) and 36 in the intervention group. Mean age of patients was 54.15 ± 15.2 in the control

group versus 53.25 ± 15.1 in the intervention group. There were 54.3% versus 41.7% females in the respective groups ($p = 0.25$). Mean body mass index was greater than 30 kg/m². More than 90% of patients were in shock with similar APACHE IV scores (53.17 ± 21.2 vs 60.38 ± 21.2) indicating severely ill ICU population. Etiology of ARDS was similar between both the groups, which include bacterial or viral pneumonia (76.1% vs 69.4%), aspiration of gastric contents (10.9% vs 13.9%), transfusion-related acute lung injury (4.3% vs 0.0%), pancreatitis (0.0% vs 2.8%), and unknown (8.7% vs 13.9%). In two third of the patients, paralytics were initiated within 48 hours of the ARDS diagnosis. The mean PaO₂/Fio₂ ratios between the groups was not significantly different (73.33 ± 22.9 vs 87.75 ± 30.5 ; $p = 0.39$). There was a trend toward higher net steroid use (converted to equivalent methylprednisolone) in the control group; however, this was not statistically significant ($676.15 \pm 1,253.8$ vs 282.62 ± 601.9 mg; $p = 0.06$). These findings are summarized in **Table 2**. More than half of the patients underwent prone positioning in both arms (54.3% vs 61.1%; $p = 0.54$), and inhaled nitric oxide use was also similar between the groups (58.7% vs 44.4%; $p = 0.2$). Extracorporeal membrane oxygenation was used in four patients (8.7%) in the control arm and one patient (2.8%) in the intervention arm ($p = 0.27$). The compliance with the study protocol in intervention group was more than 90%.

Primary Outcomes

Compared with the control group, the time to reach goal paralysis in the intervention group was shorter (8.55 ± 9.4 vs 2.63 ± 5.9 hr; $p < 0.0001$) using a

TABLE 2.
Baseline Characteristics of the Study Groups

Characteristics	Control Group (n = 46), Mean ± SD	Intervention Group (n = 36), Mean ± SD	p
Age (yr)	54.15 ± 15.2	53.25 ± 15.1	0.79
Female sex (%)	54.3	41.7	0.25
Body mass index (kg/m ²)	33.14 ± 10.8	34.16 ± 10.6	0.67
Acute Physiology and Chronic Health Evaluation IV	53.17 ± 21.2	60.38 ± 21.2	0.13
Etiology of acute respiratory distress syndrome			
Viral or bacterial pneumonia (%)	76.1	69.4	0.27
Aspiration (%)	10.9	13.9	0.52
Unknown (%)	8.7	13.9	0.27
Paralytics initiated within 48 hr (%)	78.1	83.3	0.59
Shock (%)	93.5	94.4	0.86
PaO ₂ /FiO ₂ ratio	73.33 ± 22.9	87.75 ± 30.5	0.39
Net steroid (mg of methylprednisolone)	676.15 ± 1,253.8	282.62 ± 601.9	0.06

significantly lower dose of cisatracurium (total dose of 1,897.96 ± 1,241.0 vs 562.72 ± 546.7 mg; $p < 0.0001$) at a lower rate (5.84 ± 2.66 vs 1.99 ± 0.95 µg/kg/min; $p < 0.0001$). The nonparametric Kaplan-Meier curves for the two groups are shown in **Figure 2**. The results from the log-rank test showed statistically significant difference in the time-to-goal paralysis probabilities at any time point for the two groups ($\chi^2 = 7.46$, $p = 0.0063$); HR (intervention vs control) = 2.06 (95% CI, 1.03–4.13; $p = 0.0417$). Patients in both groups remained on paralytics for approximately 2 days (57.36 ± 30.3 vs 46.97 ± 30.7 hr; $p = 0.13$).

Secondary Outcomes

The number of patients with RASS at goal prior to starting NMBA was significantly higher in the intervention group (18 [39.1%] vs 29 [80.6%]; $p \leq 0.001$). The protocol implementation was able to achieve deeper sedation at the time of initiation of NMBA (mean RASS -3.3 ± 1.9 vs -4.3 ± 1.7; $p = 0.015$). Except for the higher net use of ketamine (1.61 ± SD vs 707.73 ± SD mg; $p = 0.001$) in the intervention group, the doses of sedatives/analgesic (midazolam, propofol, dexmedetomidine, fentanyl) were similar between the groups. There was no significant difference in total time on

mechanical ventilation, length of ICU stay, or length of hospital stay between the two groups. More than half of the patients died in both groups (54.3% vs 52.8%; $p = 0.89$). There were no adverse events noted secondary to the initiation of the standardized protocol. **Table 3** describes the outcome measures.

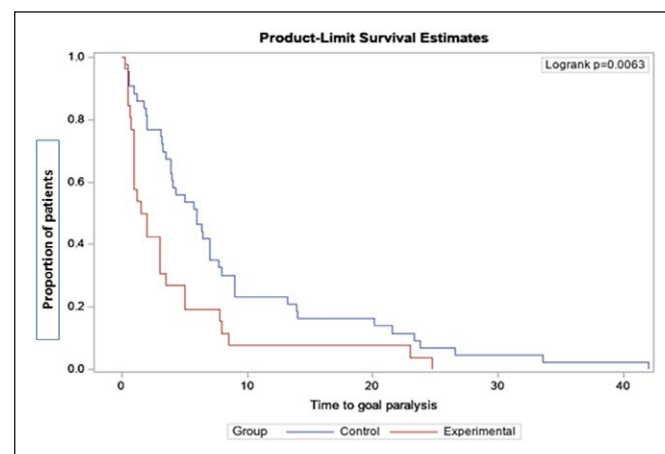


Figure 2. Kaplan-Meier Curves plots of probability of the outcome (time-to-goal paralysis) for the two groups. The log-rank test shows that the time-to-goal paralysis is significantly different between the intervention and the control groups ($\chi^2 = 7.46$; $p = 0.0063$).

TABLE 3.
Clinical, Pharmacologic, and Cost-Based Outcome Measures Between the Study Groups

Outcome Measure	Control Group (n = 46), Mean ± SD	Intervention Group (n = 36), Mean ± SD	p
Time to goal paralytic (hr)	8.55 ± 9.4	2.63 ± 5.9	< 0.001
Time on paralytics (hr)	57.36 ± 30.3	46.97 ± 30.7	0.13
Hospital length of stay (d)	18.81 ± 16.0	17.73 ± 13.3	0.74
ICU length of stay (d)	10.75 ± 7.49	9.81 ± 7.4	0.57
Time on mechanical ventilation (d)	8.75 ± 5.75	8.91 ± 8.6	0.92
RASS -5 before starting neuromuscular blocking agent, n (%)	18 (39.1)	29 (80.6)	< 0.001
Mean RASS	-3.3 ± 1.9	-4.3 ± 1.7	0.015
Total midazolam (mg) ^a	236.08 ± 273	240.82 ± 337.1	0.95
Total fentanyl (mg) ^a	10.38 ± 7.3	9.15 ± 6.8	0.43
Total propofol (mg) ^a	2,179.4 ± 3,647.2	3,573 ± 7,232.0	0.3
Total dexmedetomidine (µg) ^a	0.409 ± 1.0	0.199 ± 0.65	0.25
Total ketamine (mg) ^a	1.61	707.73	0.001
Total sedative cost (\$)	284.82 ± 190.4	276.70 ± 214.2	0.86
Total cisatracurium (mg)	1,897.96 ± 1,241.0	562.72 ± 546.7	< 0.001
Cisatracurium (µg/kg/min)	5.84 ± 2.66	1.99 ± 0.95	< 0.001
Paralytic cost (\$)	865.47 ± 565.90	256.59 ± 249.31	< 0.001
Total drug cost	1,150.29 ± 714.8	533.3 ± 408.26	< 0.001
Death, n (%)	25 (54.3)	19 (52.8)	0.89

RASS = Richmond Agitation and Sedation Scale.

^aSedative and analgesic doses were calculated during the duration of mechanical ventilation.

Boldface values indicate statistical significance.

Resource Utilization

Total sedative cost was similar in both arms. However, the paralytic cost was significantly reduced in the intervention arm (\$865.47 vs \$256.59; $p < 0.0001$), and therefore, the protocol implementation was able to save \$616.99 in total drug cost per patient (\$1,150.29 vs \$533.3; $p < 0.0001$).

DISCUSSION

Effective NMBA management has challenged clinicians for decades despite its frequent use in clinical practice (15). Rhoney et al (16) showed that use of NMBAs was

prolonged beyond 72 hours in 10–20% of ICU patients, whereas other studies have shown paralytic usage in up to 40% of ventilated patients (17). However, the use of NMBAs has inherent risks, particularly when providers are unfamiliar with the nuances of selecting the appropriate agent, monitoring the depth of neuromuscular blockade, and ensuring adequate skeletal muscle recovery once NMBA therapy has ceased. Concomitant use of systemic corticosteroids and continuous NMBA for greater than 48 hours have been associated with increased risk of ICU-acquired weakness (18). Monitoring the depth of neuromuscular blockade in ICU patients is recommended as it may minimize

adverse events. Our proof-of-concept study using clinical variable-based protocol for NMBA titration and monitoring was successful in achieving earlier goal paralysis with reduced total dose of paralytic agent and deeper sedation prior to starting NMBA.

Most commonly, depth of paralysis is assessed by use of electrical stimulation of a peripheral nerve and observing the response (aka “twitch monitoring”). TO monitor is one of the commonly used peripheral nerve stimulators to evaluate the degree of neuromuscular blockade. After delivery of four successive stimulating currents to a select peripheral nerve, the number of twitches correlates with the degree of neuromuscular blockade. However, peripheral nerve stimulators can be unreliable in the critically ill patient due to edema, perspiration, electrode nonadhesion, and lack of euthermia (19). There are technical and practical difficulties in using PNS that require training and optimal patient conditions for accuracy, leading to a great deal of interrater and intrarater variability during examination (19, 20). Use of nerve stimulation techniques for monitoring the depth of blockade and adjusting drug doses in continuously paralyzed critical ill patients has yielded mixed results in comparison to clinical assessment alone (21–23).

The physiologic reasoning behind the use of NMBA in severe ARDS patients includes improvement in patient-ventilator dyssynchrony, work of breathing, and compliance (5). Rather than solely using indirect method of paralysis (i.e., PNS), which has been shown to be unreliable (24), this study attempts to add direct method of determining neuromuscular blockade through spontaneous breathing, cough, and gag reflex evaluation. Establishing an evidence-based protocol that integrates the clinical variables and TOF assessments could serve as an optimal strategy for the titration and monitoring of NMBA in ARDS. A similar approach has been recommended by various professional societies for management of NMBAs in critically ill patients (25).

Unintended awareness and recall are also a major concern during the use of NMBAs (26). The exact combination of sedation and analgesia to prevent this is not known in patients receiving continuous NMBA, but setting the standard RASS score of -5 before starting the NMBA may provide optimal sedation rather than relying only on a single monitor (BIS). In our study, we achieved adequate and deep sedation prior to initiation of NMBA. Ketamine usage was significantly higher in the intervention group compared with

tradition sedatives and analgesics. The utility of ketamine as opioid and benzodiazepine sparing agent in multiple disease states have played a role in the reemergence of ketamine in critically ill patients (27).

Our findings represent the effort of an institution-based standardized protocol implemented systematically with education of ICU providers including nurses, respiratory therapists, pharmacists, and physicians. Bedside teaching and weekly hands-on workshops were done to ensure clinical assessment of depth of sedation along with paralysis titration and monitoring were consistent as per the protocol. Quarterly workshops for ICU staff are done throughout the year to ensure the protocol is followed properly.

Because of the high cost of ICU care, healthcare providers and hospital administration often face the dilemma of meeting an increased demand for healthcare services within financial constraints of the institute (28). Medications contribute significantly to the cost of ICU care (29). With successful implementation of our protocol for mechanically ventilated ARDS patients in the intervention arm, we were able to demonstrate cost reduction from lesser amount of total NMBA use. The severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 [COVID-19]) epidemic has brought with it many challenges including the issue of drug shortages. With many COVID-19 patients requiring NMBA for the treatment of ARDS, the need to reserve drug and minimize cost is imperative. Our study demonstrates a method that can be used to conserve drug and cost while maintaining outcomes for ARDS patients.

Our study design has several limitations. It is a single academic medical center study. This may limit the external validity of our findings to community-based hospitals with varied practices for use of NMBA. Our study patients were predominantly White; therefore, the impact on racial and ethnic minority population needs to be studied. The use of the protocol for non-ARDS critically ill patients remains unclear as we included only the patients with severe ARDS. Our trial used cisatracurium, so our data may not be generalizable to ICUs that use other agents such as rocuronium or vecuronium. The cost and choice of the neuromuscular blockade is widely variable across institutions; therefore, significant cost reduction as seen in our study may not be as significant for other institutions. One of the limitations of using historic controls entails changes in medical practice over time that may confound the association. To overcome this limitation,

the historic control data time points were selected in close proximity to the data collection period of the intervention group (within a year). Standard of care including ARDS Network protocol, severity of patients' illness, or any other standard policy related to ARDS patients care did not change during the study period. We are confident that the secular changes overtime in care unrelated to NMBA policy change would be applicable to both groups. Lower doses of neuromuscular agents may reduce the risk of prolonged neuromuscular weakness, but we did not address this issue in our study because the information on neuromuscular weakness in historical control was not consistent or standardized. Last, we cannot completely rule out the bias introduced because of protocol implementation in the intervention group as it may influence intensivists' practice for NMBA titration and cessation compared with the control group. Larger prospective studies are needed to confirm these findings and provide insight into the ICU resource utilization.

CONCLUSIONS

Implementation of comprehensive healthcare providers education, standardization of sedation prior to NMBA initiation, integration of clinical goals of paralytic administration (lack of cough and gag reflex and spontaneous breathing over the ventilator), and TOF assessments serve as optimal strategies for the titration and monitoring of NMBA in ARDS. This resulted in reduced drug utilization while continuing to achieve benefit, which reduces ICU costs and may help reduce post-ICU morbidity.

ACKNOWLEDGMENTS

We thank Prasoon Jain, MD, and Thomas O. Patrick for the critical reading of the article.

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The study protocol was approved by the institutional review board of West Virginia University (Protocol Number: 1904535385).

All data generated or analyzed during this study are included in this published article.

Dr. Hadique takes the responsibility of the content of the article, including the data and analysis. Drs. Hadique, Badami, Forte, Kovacic, Umer, and Shigle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Hadique, Badami, Forte, Kovacic, Shigle, Gardo, and Sangani contributed substantially to the study design. Drs. Hadique, Badami, Forte, Kovacic, Umer, Shigle, and Sangani contributed toward the writing of article. All authors have read and approved the article.

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The authors have disclosed that they do not have any potential conflicts of interest.

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