Early Neuromuscular Blockade in Moderate-to-Severe Pediatric Acute Respiratory Distress Syndrome

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OBJECTIVES: The use of neuromuscular blocking agents (NMBAs) in pediatric acute respiratory distress syndrome (PARDS) is common but unsupported by efficacy data. We sought to compare the outcomes between patients with moderate-to-severe PARDS receiving continuous NMBA during the first 48 hours of endotracheal intubation (early NMBA) and those without.

DESIGN: Secondary analysis of data from the Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) clinical trial, a pediatric multicenter cluster randomized trial of sedation.

SETTING: Thirty-one PICUs in the United States.

PATIENTS: Children 2 weeks to 17 years receiving invasive mechanical ventilation (MV) for moderate-to-severe PARDS (i.e., oxygenation index ≥ 8 and bilateral infiltrates on chest radiograph on days 0–1 of endotracheal intubation).

INTERVENTIONS: NMBA for the entire duration of days 1 and 2 after intubation.

MEASUREMENTS AND MAIN RESULTS: Among 1,182 *RESTORE* patients with moderate-to-severe PARDS, 196 (17%) received early NMBA for a median of 50.0% ventilator days (interquartile range, 33.3–60.7%). The propensity score model predicting the probability of receiving early NMBA included high-frequency oscillatory ventilation on days 0–2 (odds ratio [OR], 7.61; 95% CI, 4.75–12.21) and severe PARDS on days 0–1 (OR, 2.16; 95% CI, 1.50–3.12). After adjusting for risk category, early use of NMBA was associated with a longer duration of MV (hazard ratio, 0.57; 95% CI, 0.48–0.68; $p < 0.0001$), but not with mortality (OR, 1.62; 95% CI, 0.92–2.85; $p = 0.096$) compared with no early use of NMBA. Other outcomes including cognitive, functional, and physical impairment at 6 months post-PICU discharge were similar. Outcomes did not differ when comparing high versus low NMBA usage sites or when patients were stratified by baseline Pao_2/Fio_2 less than 150.

CONCLUSIONS: Early NMBA use was associated with a longer duration of MV. This propensity score analysis underscores the need for a randomized controlled trial in pediatrics.

KEY WORDS: acute lung injury; acute respiratory distress syndrome; acute respiratory failure; children; neuromuscular blocking agents; pediatric intensive care

A decade ago, neuromuscular blocking agents (NMBAs) were identified as one of the few therapeutic drug modalities that could improve patient outcomes in moderate-to-severe acute respiratory distress syndrome (ARDS). Papazian et al (1) demonstrated improved 90-day survival and increased time off the ventilator without increased muscle weakness with the early use of cisatracurium among adults with moderate-to-severe ARDS ($Pao_2/Fio_2 < 150$) in the ARDS et Curarisation Systematique (ACURASYS) trial. These findings remained consistent when combined in a meta-analysis

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with earlier, smaller studies from the same group of investigators (2). Additional beneficial effects of NMBA observed included sustained improvement in oxygenation, less organ dysfunction, and a lower pro-inflammatory response (3–5). The practice change that followed this trial came under scrutiny after publication of the Reevaluation Of Systemic Early Neuromuscular Blockade (ROSE) trial in 2019 (6). This trial was designed to determine the safety and efficacy of early NMBA with concomitant heavy sedation compared with a strategy of usual care with lighter sedation targets. However, the ROSE trial was prematurely terminated for futility after the inclusion of 1,006 patients because no differences in 90-day survival (42.5% vs 42.8%) were seen.

In the absence of clinical evidence, the Pediatric Acute Lung Injury Consensus Collaborative (PALICC) recommended considering NMBA when sedation alone is inadequate to achieve effective mechanical ventilation (MV) and that further studies are needed to better understand the short- and long-term outcomes of NMBA use in children (7). We used the Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) data to compare the short-term (amount of sedatives, extracorporeal membrane oxygenation) and long-term (length of MV, mortality, cognitive and functional impairment at discharge, cognitive, functional, and physical impairment at 6 mo post-discharge) outcomes in patients who received NMBA for the entire duration of days 1 and 2 after intubation to those patients who did not (8).

METHODS

We performed a secondary analysis of the *RESTORE* dataset (8). *RESTORE* was a 31-center cluster randomized clinical trial that enrolled pediatric patients, 2 weeks to 17 years old, intubated and ventilated for acute respiratory failure from airways and parenchymal disease between 2009 and 2013. Thirty-one PICUs were randomized to either usual care or a protocol that included targeted sedation, arousal assessments, extubation readiness testing, sedation adjustment every 8 hours, and sedation weaning. Patients expected to be extubated within 24 hours were excluded. Written informed consent was obtained from the legal guardian of each subject. Other than using the sedation protocol at intervention PICUs, no other aspect of care was prescribed by study protocol. Decisions about MV mode, use of NMBA, and ventilator weaning strategy were at the discretion of the treating clinical care team. The institutional review board (IRB) of the University of Pennsylvania approved the trial (IRB approval number 808830).

We identified patients with moderate-to-severe pediatric ARDS (PARDS) by an oxygenation index (OI) ([mean airway pressure (mPaw) × F_{IO_2} × 100]/Pa_{O_2}) greater than or equal to 8 and bilateral infiltrates on chest radiograph on days 0–1 of endotracheal intubation. Transcuteanous oxygen saturation (Sp_{O_2}) was used to estimate Pa_{O_2} in order to calculate oxygen saturation index (OSI) ([mPaw × F_{IO_2} × 100]/Sp_{O_2}) when no indwelling arterial line was present (9). OI and OSI were calculated based on worst daily values on the day of endotracheal intubation/PICU admission (day 0) and daily values closest to 08:00. In this cohort, patients were stratified by early NMBA (i.e., receiving NMBA for the entire duration of days 1 and 2 after intubation) or not (i.e., not receiving NMBA for the entire duration of days 1 and 2 after intubation) to best reflect the treatment group allocation (continuous NMBA for 48 hr or not) in the ACURASYS clinical trial (1).

Analyses focused on comparing outcomes of patients who received early NMBA compared with those who did not. The primary outcomes for this analysis were duration of MV through 28 days and inhospital mortality at day 90. Patients were assigned 28 days of MV if they remained intubated, were transferred, or died before day 28 without remaining extubated for 24 hours, therefore making this outcome equivalent to ventilator-free days (10). Secondary outcomes included time to recovery from acute respiratory failure (intubation to time first qualifying for an extubation readiness test), duration of weaning from MV (time first qualifying for an extubation readiness test to successful extubation), ECMO use after day 2, peak daily opioid and benzodiazepine dose, cognitive and functional impairment at hospital discharge, and cognitive, functional, and physical impairment at 6 months post-PICU discharge. Cognitive and functional impairments were defined as Pediatric Cerebral Performance Category greater than 1 and Pediatric Overall Performance Category greater than 1, respectively (8, 11, 12). Physical impairment was defined as Infant and Toddler Quality of Life Questionnaire

(ITQOL) physical abilities score or Pediatric Quality of Life Inventory (PedsQL) physical functioning score greater than 1 SD below the mean of the reference population (13, 14). ITQOL was completed by parents/guardians for children less than 2 years old or children greater than or equal to 2 years old with developmental impairment, and PedsQL was completed by parents/guardians for children greater than or equal to 2 years old without developmental impairment. Organ dysfunction on days 0–1 was also calculated (15).

Patient characteristics were compared across groups using logistic, linear, or cumulative logit regression for binary, log-transformed continuous, and ordinal variables, respectively. Analyses of outcome data used these methods and proportional hazards regression for length of time variables. All regression analysis accounted for PICU as a cluster variable using generalized estimating equations (16). Duration of MV was analyzed using proportional hazards regression analysis and Kaplan-Meier curves. Site variability in early NMBA was evaluated by calculating the intraclass correlation coefficient (ICC) from an analysis of variance adjusting for age group and Pediatric Risk of Mortality (PRISM) III-12 score, with CIs constructed using Searle's method to adjust for unequal sample sizes across sites (17, 18). NMBA usage (any) by site ranged from 8.6% to 70.8% of enrolled patients with a cluster of 12 sites using NMBA in greater than 25% of enrolled patients. We defined these sites as high NMBA usage sites.

Propensity score matching was used to address confounding by indication by accounting for covariates predicting early NMBA use (19). A stepwise multivariable logistic regression analysis adjusting for age group and PRISM III-12 score (12) was used to generate a model estimating the probability of early NMBA use by including variables with p value of less than 0.05 in univariate analyses. Fitted probabilities (i.e., the propensity scores) from the model were then used to stratify patients into quintiles. First, we assessed the effects of early NMBA on outcomes adjusting for risk category based on these quintiles. Second, we assessed the effects of early NMBA on outcomes in analyses stratified by quintiles. These analyses focused on quintiles 4 and 5, the quintiles of highest risk of early NMBA (20). Additional analyses compared outcomes according to early versus late (NMBA initiated after day 2) NMBA, high versus low NMBA usage site, and early versus no early NMBA stratified by worst Pao_2/Fio_2 ratio on days 0–1 (< 150 or ≥ 150). Data analyses were performed using Statistical Analysis Software (SAS) Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Among the 2,449 patients enrolled in *RESTORE*, 1,207 (49%) had moderate-to-severe PARDS and bilateral infiltrates on days 0–1. Of these, 25 patients (2%) on ECMO between days 0 and 2 were excluded, leaving 1,182 patients for analysis. In this cohort, 196 patients (17%) received early NMBA (entire duration of days 1–2) for a median of 50.0% ventilator days (interquartile range [IQR], 33.3–60.7%) and a median of 5 study days (IQR, 3–9.5). Site variability of early NMBA ranged from 0% to 60.6% patients in this cohort with a median of 12.9% (IQR, 4.0–21.2%). This yielded an ICC of 0.102 (95% CI, 0.061–0.177), indicating strong variation in early NMBA use by site. Of the 986 patients in the no early NMBA group, 733 (74%) did not receive any NMBA, 80 (8%) received NMBA on day 1 or day 2 only, 68 (7%) received NMBA on day 1 or day 2 and also after day 2, and 105 (11%) received late NMBA (initiated after day 2).

Table 1 summarizes baseline characteristics stratified by early versus no early NMBA use. Patients who received early NMBA were older and sicker with higher risk of mortality. A higher proportion of early NMBA patients had parenchymal disease, current or past diagnosis of cancer, or a chromosomal abnormality. There was no difference in the use of early NMBA in patients in the *RESTORE* intervention versus usual care sites. Whereas half of those who did not receive early NMBA had severe PARDS on days 0–1 (n = 511, 52%), the majority of patients who received early NMBA had severe PARDS (n = 156, 80%). The worst OI on days 0–1 was significantly higher in the early NMBA group (median, 25.0 [IQR, 16.1–36.7] vs 15.1 [10.6–22.5]), and these patients were more likely to be supported on HFOV on days 0–2 (52% vs 10%; $p < 0.0001$). Patients in the early NMBA group also had more organ dysfunction on days 0–1, including cardiovascular (70% vs 42%), neurologic (44% vs 38%), and hematologic dysfunction (26% vs 16%).

The propensity score analysis identified multiple risk factors predicting the probability of receiving early NMBA (**Supplemental Table 1**, http://links.lww.com/CCM/G932). Specifically, HFOV

TABLE 1.
Patient Characteristics According to Group

Variable	Early NMBA (*n* = 196)	No Early NMBA (*n* = 986)	*p*[a]
Age at PICU admission			
Median (IQR), yr	3.6 (1.0–12.1)	2.5 (0.5–8.7)	0.0096
n (%)			0.12
2 wk to < 2 yr	81 (41)	459 (47)	
2 to < 6 yr	35 (18)	199 (20)	
6 to < 18 yr	80 (41)	328 (33)	
Female	89 (45)	464 (47)	0.70
Non-Hispanic White	98/195 (50)	531/981 (54)	0.44
Normal functional status at baseline	138 (70)	688 (70)	0.34
PRISM III-12 score	10 (5–17.5)	8 (3–13)	< 0.0001
Risk of mortality based on PRISM III-12 score, %	7.5 (1.7–31.3)	4.3 (1.3–14.2)	< 0.0001
Any medical history			
Prematurity (< 36 wk postmenstrual age)	32 (16)	168 (17)	0.82
Asthma (prescribed bronchodilators or steroids)	25 (13)	140 (14)	0.52
Seizure disorder (prescribed anticonvulsants)	16 (8)	94 (10)	0.51
Cancer (current or previous diagnosis)	30 (15)	99 (10)	0.029
Known chromosomal abnormality	17 (9)	47 (5)	0.0047
Primary diagnosis category			0.00090
Airways disease	39 (20)	318 (32)	
Parenchymal disease	157 (80)	668 (68)	
Randomized Evaluation of Sedation Titration for Respiratory Failure intervention group	100 (51)	502 (51)	0.48
Worst OI on days 0–1[b]	25.0 (16.1–36.7)	15.1 (10.6–22.5)	< 0.0001
Worst OSI on days 0–1[b]	16.3 (10.7–27.5)	11.7 (8.7–17.1)	0.00077
Pediatric acute respiratory distress syndrome based on worst OI/OSI on days 0–1			< 0.0001
Moderate (OI 8.0–15.9 or OSI 7.5–12.2)	40 (20)	475 (48)	
Severe (OI ≥ 16.0 or OSI ≥ 12.3)	156 (80)	511 (52)	
Worst Pao_2/Fio_2 ratio on days 0–1[b]	79 (57–110)	99 (74–134)	< 0.0001
Organ dysfunction on days 0–1			
Median (IQR), number of organ dysfunctions	3 (2–3)	2 (1–3)	< 0.0001
n (%)			
Cardiovascular	137 (70)	412 (42)	< 0.0001
Neurologic	87 (44)	375 (38)	0.00023
Hematologic	50 (26)	161 (16)	0.00088
Hepatic	40 (20)	154 (16)	0.019
Renal	12 (6)	47 (5)	0.36

IQR = interquartile range, NMBA = neuromuscular blocking agent, OI = oxygenation index, OSI = oxygen saturation index, PRISM III-12 = Pediatric Risk of Mortality III score from first 12 hr in the PICU.

[a]*p* values for comparison between groups were calculated using linear, cumulative logit, and logistic regression accounting for PICU as a cluster variable using generalized estimating equations for log-transformed continuous, ordinal, and binary variables, respectively.

[b]Worst OI calculated for 185 early NMBA and 676 no early NMBA patients. Worst OSI calculated for 55 early NMBA and 545 no early NMBA patients. Worst Pao_2/Fio_2 ratio calculated for 185 early NMBA and 677 no early NMBA patients.

Data are median (IQR), *n* (%), or *n*/*n* (%). Denominators are shown where data are missing.

on days 0–2 (odds ratio [OR], 7.61 [95% CI, 4.75–12.21]), severe PARDS on days 0–1 (OR, 2.16 [95% CI, 1.50–3.12]), and cardiovascular organ dysfunction on days 0–1 (OR, 1.68 [95% CI, 1.25–2.25]) were associated with early NMBA use. **Table 2** and **Supplemental Table 2** (http://links.lww.com/CCM/G933) compare the characteristics of patients by propensity score quintile (the two quintiles of lowest risk were combined because of small numbers of patients receiving early NMBA) demonstrating distinctive pattern differences by quintile. Duration of MV was significantly longer in patients receiving early NMBA compared with no early NMBA, irrespective of quintile stratum (**Table 3** and **Fig. 1**). Time to recovery from acute respiratory failure was significantly prolonged in patients receiving early NMBA in quintile 4. Inhospital mortality at 90 days was not different between those with and without early NMBA. Other outcomes including

TABLE 2.
Patient Characteristics According to Propensity Score Quintile

Variable	Quintile 5 (Highest Risk of Early NMBA) (*n* = 237)	Quintile 4 (*n* = 235)	Quintile 3 (*n* = 237)	Quintiles 1–2 (Lowest Risk of Early NMBA) (*n* = 473)	*p*[a]
Fitted probabilities	0.50 (0.37–0.57)	0.14 (0.12–0.15)	0.09 (0.09–0.09)	0.04 (0.04–0.07)	< 0.0001
Early NMBA	110 (46)	32 (14)	28 (12)	26 (6)	< 0.0001
Age at PICU admission					
Median (IQR), yr	4.4 (1.0–12.0)	6.2 (1.6–12.6)	1.6 (0.5–10.4)	1.6 (0.4–4.8)	< 0.0001
n (%)					< 0.0001
2 wk to < 2 yr	85 (36)	64 (27)	132 (56)	259 (55)	
2 to < 6 yr	45 (19)	50 (21)	13 (5)	126 (27)	
6 to < 18 yr	107 (45)	121 (51)	92 (39)	88 (19)	
Female	116 (49)	119 (51)	111 (47)	207 (44)	0.16
Non-Hispanic White	127/235 (54)	136/234 (58)	128/236 (54)	238/471 (51)	0.0074
Normal functional status at baseline	160 (68)	149 (63)	166 (70)	351 (74)	0.022
PRISM III-12 score	13 (5–22)	11 (7–16)	6 (3–13)	6 (3–10)	< 0.0001
Risk of mortality based on PRISM III-12 score, %	15.3 (2.9–53.5)	9.5 (3.6–23.5)	3.4 (1.0–11.7)	2.3 (1.0–6.4)	< 0.0001
Any medical history					
Prematurity (< 36 wk postmenstrual age)	31 (13)	34 (14)	49 (21)	86 (18)	0.072
Asthma (prescribed bronchodilators or steroids)	22 (9)	28 (12)	31 (13)	84 (18)	0.00070
Seizure disorder (prescribed anticonvulsants)	24 (10)	29 (12)	24 (10)	33 (7)	0.018
Cancer (current or previous diagnosis)	49 (21)	35 (15)	22 (9)	23 (5)	< 0.0001
Known chromosomal abnormality	17 (7)	17 (7)	7 (3)	23 (5)	0.057

(*Continued*)

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Patient Characteristics According to Propensity Score Quintile

Variable	Quintile 5 (Highest Risk of Early NMBA) (*n* = 237)	Quintile 4 (*n* = 235)	Quintile 3 (*n* = 237)	Quintiles 1–2 (Lowest Risk of Early NMBA) (*n* = 473)	*p*[a]
Primary diagnosis category					< 0.0001
Airways disease	33 (14)	35 (15)	80 (34)	209 (44)	
Parenchymal disease	204 (86)	200 (85)	157 (66)	264 (56)	
Randomized Evaluation of Sedation Titration for Respiratory Failure intervention group	112 (47)	113 (48)	133 (56)	244 (52)	0.28
Worst OI on days 0–1	26.5 (18.5–40.0)	22.9 (17.8–28.7)	16.5 (11.7–20.9)	11.2 (9.1–13.6)	< 0.0001
Worst OSI on days 0–1	19.3 (12.5–33.3)	20.0 (14.0–24.2)	14.5 (12.6–19.4)	9.3 (7.7–11.0)	< 0.0001
Pediatric acute respiratory distress syndrome based on worst OI/OSI on days 0–1					< 0.0001[b]
Moderate (OI 8.0–15.9 or OSI 7.5–12.2)	34 (14)	0	46 (19)	435 (92)	
Severe (OI ≥ 16.0 or OSI ≥ 12.3)	203 (86)	235 (100)	191 (81)	38 (8)	
Worst Pao_2/Fio_2 ratio on days 0–1	78 (57–111)	74 (60–96)	94 (70–134)	122 (98–151)	< 0.0001
Organ dysfunction on days 0–1					
Median (IQR), number of organ dysfunctions	3 (2–4)	3 (2–3)	2 (1–2)	2 (1–2)	< 0.0001
n (%)					
Cardiovascular	184 (78)	196 (83)	46 (19)	123 (26)	< 0.0001
Neurologic	131 (55)	97 (41)	79 (33)	155 (33)	< 0.0001
Hematologic	79 (33)	53 (23)	39 (16)	40 (8)	< 0.0001
Hepatic	78 (33)	44 (19)	28 (12)	44 (9)	< 0.0001
Renal	19 (8)	16 (7)	9 (4)	15 (3)	0.0017

IQR = interquartile range, NMBA = neuromuscular blocking agent, OI = oxygenation index, OSI = oxygen saturation index, PRISM III-12 = Pediatric Risk of Mortality III score from first 12 hr in the PICU.

[a]*p* values for comparison between groups were calculated using linear, logistic, and cumulative logit regression accounting for PICU as a cluster variable using generalized estimating equations for log-transformed continuous, binary, and ordinal variables, respectively.

[b]Due to zero counts, *p* values from exact logistic regression not accounting for PICU as a cluster variable.

Data are median (IQR), *n* (%), or *n*/*n* (%). Denominators are shown where data are missing.

TABLE 3.
Outcomes According to Propensity Score Quintile (4 or 5) and Group

Outcome	Quintile 5 (Highest Risk of Early NMBA)			Quintile 4		
	Early NMBA ($n = 110$)	No Early NMBA ($n = 127$)	p[a]	Early NMBA ($n = 32$)	No Early NMBA ($n = 203$)	p[a]
Duration of mechanical ventilation through day 28, d[b]	15.1 (9.5–28.0)	10.8 (6.6–16.8)	0.0097	11.6 (9.1–18.9)	7.0 (4.5–12.3)	0.0001
Time to recovery from acute respiratory failure, d[c]	10.0 (6.4–14.7)	6.6 (4.2–11.4)	0.050	8.3 (6.4–10.2)	3.4 (2.2–6.5)	< 0.0001
Duration of weaning from mechanical ventilation, d[d]	2.1 (1.1–4.4)	2.2 (0.4–4.1)	0.50	2.3 (1.1–3.8)	2.2 (1.1–4.3)	0.32
Inhospital mortality at 90 d	20 (18)	18 (14)	0.41	5 (16)	17 (8)	0.16
Extracorporeal membrane oxygenation after day 2	6 (5)	3 (2)	0.26	1 (3)	6 (3)	0.94
Peak daily opioid dose, mg/kg	6.2 (3.5–9.8)	6.7 (3.4–10.7)	0.89	4.9 (2.9–6.6)	3.5 (2.0–7.3)	0.16
Peak daily benzodiazepine dose, mg/kg	4.5 (2.7–8.6)	4.8 (1.9–10.0)	0.28	5.2 (2.9–7.4)	2.6 (1.4–6.6)	0.013
Cognitive impairment (PCPC > 1) at hospital discharge[e]	37/86 (43)	44/104 (42)	0.80	7/26 (27)	70/181 (39)	0.19
Functional impairment (POPC > 1) at hospital discharge[e]	44/86 (51)	55/104 (53)	0.89	11/26 (42)	85/181 (47)	0.92
Discharge home by day 90[e]	73/90 (81)	92/109 (84)	0.63	23/27 (85)	160/186 (86)	0.83
Cognitive impairment (PCPC > 1) at 6 mo post-PICU discharge	16/35 (46)	16/44 (36)	0.51	1/9 (11)	26/81 (32)	0.21
Functional impairment (POPC > 1) at 6 mo post-PICU discharge	18/35 (51)	20/44 (45)	0.61	5/9 (56)	36/81 (44)	0.21
Physical impairment at 6 mo post-PICU discharge	9/26 (35)	16/43 (37)	0.81	3/10 (30)	22/67 (33)	0.91

NMBA = neuromuscular blocking agent, PCPC = Pediatric Cerebral Performance Category, POPC = Pediatric Overall Performance Category.

[a]Within each quintile, *p* values for the comparison of outcomes between groups were calculated using proportional hazards, logistic, and linear regression accounting for PICU as a cluster variable using generalized estimating equations for time-to-event, binary, and log-transformed continuous variables, respectively.

[b]Patients were assigned 28 d of mechanical ventilation if they remained intubated or were transferred or died before day 28 without remaining extubated for 24 hr, therefore making the outcome equivalent to ventilator-free days.

[c]Time to recovery from acute respiratory failure excludes nonsurvivors who did not meet criteria before death. For survivors who never met criteria, the duration of recovery was set equal to the duration of mechanical ventilation if the patient was successfully extubated or to 28 d if the patient was still intubated on day 28 or transferred to another PICU still intubated. Within quintile 5, calculated for 90 early NMBA and 112 no early NMBA patients. Within quintile 4, calculated for 28 early NMBA and 191 no early NMBA patients.

[d]Duration of weaning from mechanical ventilation excludes nonsurvivors who were not extubated for > 24 hr before death. Also excludes survivors who never met criteria or were still intubated on day 28. Within quintile 5, calculated for 74 early NMBA and 90 no early NMBA patients. Within quintile 4, calculated for 25 early NMBA and 164 no early NMBA patients.

[e]PCPC, POPC, and location at hospital discharge exclude nonsurvivors.

Data are median (interquartile range), *n* (%), or *n*/*n* (%). Denominators are shown where data are missing.

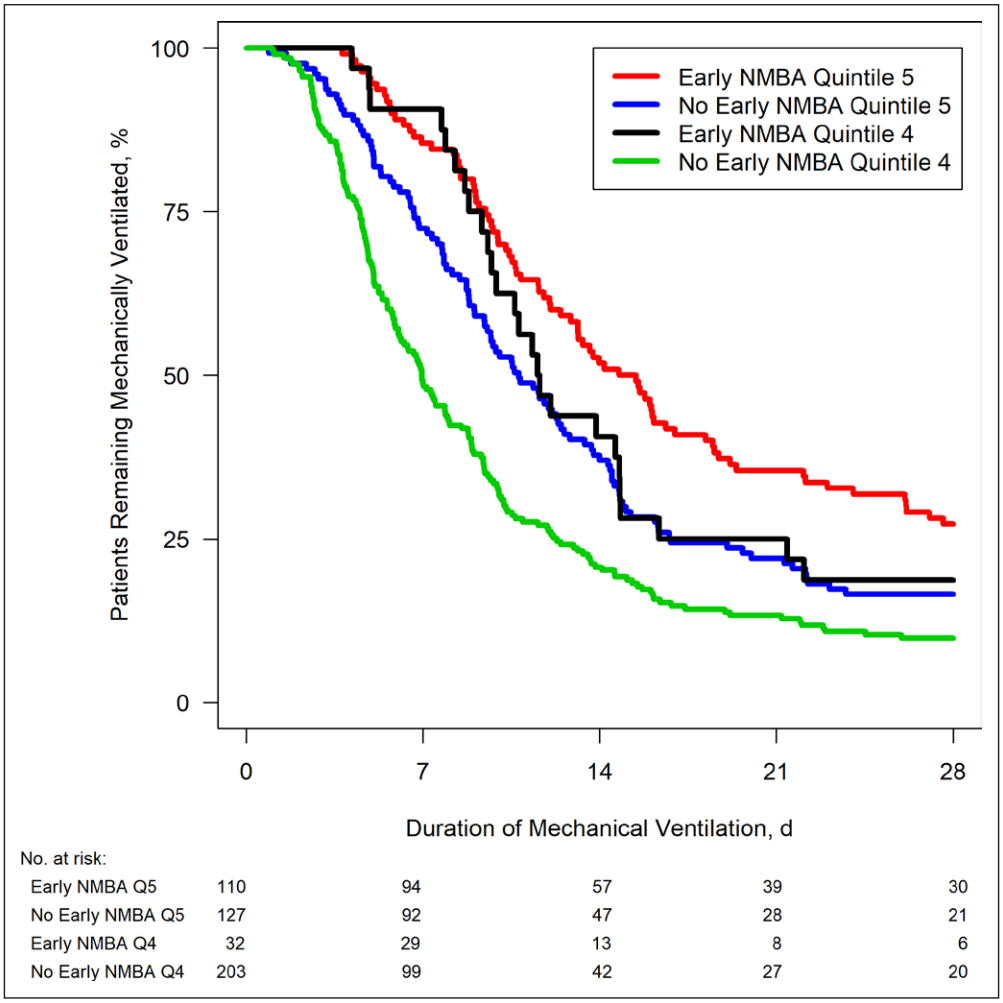

Figure 1. Duration of mechanical ventilation to day 28 by propensity score quintile (Q) and group. NMBA = neuromuscular blocking agent.

cognitive, functional, and physical impairment at 6 months post-PICU discharge were also not different between the two groups. Similar observations were made for quintiles 1–3 (**Supplemental Table 3**, http://links.lww.com/CCM/G934) and when the cohort was stratified by baseline Pao_2/Fio_2 ratio (i.e., < 150 or ≥ 150; **Supplemental Table 4**, http://links.lww.com/CCM/G935).

Across all quintiles, early use of NMBA was significantly associated with a longer duration of MV (hazard ratio [HR], 0.60; 95% CI, 0.50–0.72; $p < 0.0001$), but not with a higher risk of inhospital mortality at 90 days (OR, 1.92; 95% CI, 0.99–3.73; $p = 0.053$) after adjusting for age group, PRISM III-12 score, severe PARDS on days 0–1, cardiovascular dysfunction on days 0–1, and HFOV on days 0–2. When we adjusted for propensity score quintile only, early use of NMBA remained associated with a longer duration of MV (HR, 0.57; 95% CI, 0.48–0.68; $p < 0.0001$). The use of early NMBA was not significantly associated with mortality after adjusting for risk category (OR, 1.62; 95% CI, 0.92–2.85; $p = 0.096$). Extubation failure was not different between patients with or without early NMBA (7% vs 8%; $p = 0.45$).

Patients who received early NMBA received more days of NMBA compared with patients who received late NMBA (i.e., initiated after day 2) (median 5 vs 3.5 d; $p = 0.0077$). The majority of early NMBA patients ($n = 150$, 77%) continued to receive NMBA after day 2, and **Supplemental Figure 1** (http://links.lww.com/CCM/G936) shows the number of patients receiving NMBA by study day, according to early versus late NMBA. In unstratified analyses, patients receiving early NMBA had comparable duration of MV and inhospital mortality at 90 days compared with patients receiving late NMBA (**Supplemental Table 5**, http://links.lww.com/CCM/G937). Similar observations were made among patients who continued to receive NMBA ($n = 68$, excluding those who only received NMBA on day 1 or 2) compared with those in whom NMBAs were initiated after day 2 ($n = 105$) (**Supplemental Table 6**, http://links.lww.com/CCM/G938). However, duration of weaning from MV was prolonged in patients with late NMBA (median, 3.5 d [IQR, 1.9–6.2 d] vs 2.2 d [1.1–4.3 d]; $p = 0.0028$), and patients with late NMBA had a higher peak daily opioid dose (8.0 mg/kg [4.9–12.3 mg/kg] vs 5.8 mg/kg [3.5–8.4 mg/kg]; $p < 0.0001$) and higher peak daily benzodiazepine dose (7.8 mg/kg [3.8–14.9 mg/kg] vs 4.7 mg/kg [2.8–8.7 mg/kg]; $p = 0.0019$). However, we found fewer late NMBA patients with functional impairment at hospital discharge

(Supplemental Table 5, http://links.lww.com/CCM/G937). In addition, there were no differences in the duration of MV, inhospital mortality at 90 days, and most other outcomes between patients receiving any NMBA at high- versus low-usage NMBA sites (**Supplemental Table 7**, http://links.lww.com/CCM/G939).

DISCUSSION

This is the first and largest study reporting the outcomes of NMBA in moderate-to-severe PARDS. We observed prolonged duration of MV among patients receiving early NMBA compared with no early NMBA in stratified analyses and across all categories of risk after adjusting for risk category. Inhospital mortality at 90 days was not increased among patients receiving early NMBA compared with those not receiving NMBA. There was no difference in cognitive or functional impairment at hospital discharge or at 6 months post-PICU discharge between patients receiving early NMBA versus no early NMBA. Site characteristics (i.e., high vs low NMBA usage) did not affect patient outcomes.

The ACURASYS study in adults with severe ARDS changed the prevailing paradigm about always maintaining spontaneous breathing in ARDS (1). Spontaneous breathing in patients with moderate-to-severe ARDS may lead to large transpulmonary pressure (Ptp) swings, thereby causing patient self-inflicted lung injury (21). The beneficial effects of neuromuscular paralysis were thought to originate from various mechanisms including the disappearance of patient-ventilator dyssynchrony resulting in a lower Ptp (less barotrauma), smaller tidal volume [Vt] (less volutrauma), and lower pulmonary pro-inflammatory response (less biotrauma) (22). Experimental work confirmed that eliminating large Ptp in the presence of severe lung injury with the initiation of neuromuscular blockade resulted in lower lung inflammation (23–25). However, this initial enthusiasm for NMBA being the first drug to improve outcomes in ARDS was tempered when the most recent trial in adult ARDS could not confirm a mortality benefit of early NMBA (26). The most obvious explanation proposed for this discrepancy in outcomes has been that clinical practice changed since publication of the ACURASYS trial, in particular with using higher levels of positive end-expiratory pressure and lower levels of sedation. In adults, deeper sedation can result in reverse triggering, that is, contraction of the diaphragm triggered by a ventilator breath initiating a spontaneous breath resulting in inappropriately large Vt (27). Reverse triggering also occurs in children, but not necessarily only during deep sedation (28). Nonetheless, our results add to the debate related to the indication for NMBA. At the same time, the key question is whether the worse outcomes of early NMBA as seen in this study are related to NMBA itself or the manner in which this treatment modality was used.

Institutional variation in use of NMBA is not uncommon (29, 30). Many critical care practitioners have adopted the philosophy of maintaining spontaneous breathing in mechanically ventilated patients as much as possible. This concept is based on experimental studies and clinical observations in anesthetized adults with and without lung injury showing that Vt is directed toward the dorsal, well-perfused regions of the lung during spontaneous breathing, shunt fraction is reduced, and lung inflammation attenuated (31–36). Nonetheless, practitioners are inclined to use interventions such as NMBA in the most critically ill. Data from the Pediatric ARDS Incidence and Epidemiology study showed that approximately one of every three patients received continuous NMBA (31). NMBA use increased with PARDS severity and was more common among patients who also received inhaled nitric oxide and HFOV. These observations are in line with our findings, strengthening our propensity score modeling where HFOV on days 0–2 and PARDS severity on days 0–1 independently predicted the probability of using early NMBA. It may be postulated that high-usage NMBA sites would have better outcomes from more familiarity and experience with NMBA. However, outcomes did not differ when comparing high-usage sites with low-usage sites. Our findings do not allow for robust clinical recommendations but underscore the need for a trial evaluating outcomes of NMBA use in moderate-to-severe PARDS. At present, the Pediatric ARDS Neuromuscular Blockade Study is currently recruiting (NCT02902055).

Several explanations for the longer duration of MV in the early NMBA cohort exist. For instance, the early use of NMBA could decrease oxygen consumption of respiratory and other muscles, reducing cardiac output, increasing the mixed venous Po_2, and increasing the partial pressure of arterial oxygen when there

is severe hypoxemia. This would be consistent with one small study that demonstrated improved oxygenation after institution of NMBA, particularly in moderate-to-severe PARDS (32). The indication for NMBA in PARDS is poorly defined, leading to confounding by indication (i.e., the sickest patient is the most likely to receive a specific intervention—a type of bias that can only be fully overcome by randomization). PALICC recommended considering NMBA when sedation alone would be inadequate to achieve effective MV, although this recommendation has not been operationalized (7). Our study was not designed to explore these pathophysiological mechanisms.

Another explanation is that patients who are medically paralyzed are exposed to higher dosages of sedation and analgesic medications. Thus, there might be differences in management of patients receiving NMBA. Although recommended by PALICC, it is unclear how often a "NMBA holiday" (i.e., daily NMBA discontinuation to evaluate whether reinitiating NMBA is necessary) is performed (7). Furthermore, sedation and analgesia management is difficult when patients are paralyzed. It may be surmised that patients who are paralyzed are exposed to higher dosages of sedation and analgesic medications. In some stratified analyses, we observed that patients who received early NMBA had higher peak daily opioid and benzodiazepine doses compared to patients who did not receive early NMBA. Depth of neuromuscular paralysis can be assessed using the train-of-four method, although it is unclear how many PICUs use this neuromonitoring for titration of NMBA (33).

One of the main concerns explaining the reluctance to use NMBA is the development of critical illness polyneuropathy and myopathy (CIPNM), a phenomenon that has been observed especially in adults who are on concurrent corticosteroids or have renal failure (34). Limited data suggest the prevalence of CIPNM in children is very low (35). Furthermore, our study showed that using NMBA did not prolong the duration of weaning from MV in matched analyses.

There are important limitations of this study. NMBA use was not randomized, and these observational data do not imply a causal relationship. NMBA management varied among patients and centers. The decision to initiate continuous NMBA remained at the discretion of the bedside team. Inherently, latent variables, including unmeasured individual or institutional preferences, were uncontrolled. This may especially apply to the lack of MV protocols among the participating study sites. Importantly, we could not assess the adherence to lung-protective ventilation as a potential confounder in the present study. Propensity score modeling does not fully overcome these limitations (36). On top of that, propensity score modeling does not include clinical reasoning, thereby not providing the rationale for NMBA use in our cohort. Additionally, the approach to propensity scoring in this study did not account for a patient's trajectory of illness. The *RESTORE* dataset collected worst OI/OSI on day of intubation and daily values thereafter, hence limiting our categorization of the level of oxygenation failure at the precise time of initiation of NMBA. Furthermore, the *RESTORE* dataset did not collect ventilator (other than mPaw) or esophageal pressures, spontaneous breath rate, or degree of patient-ventilator dyssynchrony. Patient-ventilator dyssynchrony is common in mechanically ventilated children, especially ineffective triggering leading potentially to stronger patient efforts (and, thus, larger Ptp) to trigger the ventilator (37).

CONCLUSIONS

This secondary analysis of the *RESTORE* database showed that early NMBA was associated with a longer duration of MV and longer time to recovery from acute respiratory failure in moderate-to-severe PARDS. This propensity score analysis underscores the need for a randomized controlled trial in pediatrics.

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*The Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) study investigators are listed in* ***Appendix 1.***

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APPENDIX 1. RANDOMIZED EVALUATION OF SEDATION TITRATION FOR RESPIRATORY FAILURE (*RESTORE*) INVESTIGATORS

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