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Neuromuscular blocking agents for acute respiratory distress syndrome

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ABSTRACT

Acute respiratory distress syndrome (ARDS) is an acute inflammatory process that impairs the ability of the lungs to oxygenate thereby resulting in respiratory failure. Treatment of ARDS is often a multimodal approach using both nonpharmacologic and pharmacologic treatment strategies in addition to trying to reverse the underlying cause of ARDS. Neuromuscular blocking agents (NMBAs) have been prescribed to patients with ARDS as they are thought to decrease inflammation, oxygen consumption, and cardiac output and help facilitate ventilator synchrony. NMBAs have only been evaluated in patients with early, severe ARDS in three multicenter, randomized, controlled trials ($n = 432$), but have resulted in decreased inflammation and improved oxygenation, ventilator-free days, and mortality. Despite reports of NMBAs being associated with adverse effects like postparalytic quadriparesis, myopathy, and prolonged recovery, these effects have not been seen in patients receiving short courses of NMBAs for ARDS. A large multicenter, prospective, randomized, placebo-controlled trial is ongoing to confirm benefit of NMBAs in early, severe ARDS when adjusting for limitations of the previous studies. The current available literature suggests that 48 h of NMBA therapy in patients with early, severe ARDS improves mortality, without resulting in additional patient harm.

Acute respiratory distress syndrome (ARDS) is an acute inflammatory process that significantly damages the alveoli and impairs their ability to adequately supply oxygen to the rest of the body thereby resulting in acute hypoxemic respiratory failure. There is variability in the reported incidence of ARDS globally, ranging from 10 to 86 cases per 100,000 patients [1] and mortality is high with reported rates ranging from 25 to 46% based on the severity of initial hypoxemia [2]. By definition, ARDS develops within one week of exposure to a risk factor for ARDS. Risk factors that cause ARDS via direct lung injury include pneumonia, aspiration, inhalation injury, near drowning, and pulmonary contusion. Pneumonia and aspiration events are responsible for the majority of ARDS cases. Other risk factors for ARDS that cause indirect lung injury include sepsis, pancreatitis, cardiopulmonary bypass, burns, trauma, hemorrhagic shock, transfusions, and drug overdose [3,4]. Although there is no proven prevention approach, knowing the risk factors for ARDS can help providers implement early treatment strategies and aggressively treat the underlying cause of ARDS [5].

The treatment approach for ARDS is a multimodal strategy with non-pharmacologic interventions conferring the greatest mortality benefit compared to pharmacologic interventions. Treatment aimed at the underlying cause of ARDS should be the first step in the management of ARDS. A non-pharmacologic treatment approach implementing lung protective ventilation and conservative fluid management has been associated with the greatest benefit in patients with ARDS [5]. The recently published guidelines strongly recommend mechanical ventilation using low tidal volumes and lower inspiratory pressures. Other supported non-pharmacologic treatment strategies include higher positive end-expiratory pressure (PEEP) and recruitment maneuvers in patients with moderate to severe ARDS and prone positioning in patients with severe ARDS [6]. Of the pharmacologic treatment options studied in ARDS, only neuromuscular blocking agents (NMBAs) have demonstrated a mortality benefit in patients with severe ARDS [7]. The data evaluating corticosteroids in ARDS has been inconsistent [8-10] and other studied therapies have only demonstrated improvements in oxygenation that have not resulted in other clinically relevant outcomes [11]. In this review we discuss the use of NMBAs in ARDS.

1.1. Mechanism of action

In patients with ARDS, NMBAs are thought to exert their beneficial effects by decreasing lung and systemic inflammation, oxygen consumption, and cardiac output and increasing alveolar recruitment and the mixed venous O_2 and partial pressure of oxygen (PaO_2) by prohibiting the contraction of the respiratory muscles thereby decreasing their oxygen consumption [12-14]. The improvements in oxygenation related to NMBA use in patients with ARDS have also been associated with improvements in transpulmonary pressures and more homogenous regional inflation across the alveoli. NMBA use has been

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associated with less lung derecruitment during expiration, greater lung recruitment during inspiration and overall decreased expiratory muscle activity [15]. Decreases in cardiac output can also lead to a reduction in the accumulation of alveolar fluid as a result of a decrease in the pulmonary vascular pressure gradient. In patients with ARDS, NMBAs are also thought to exert their beneficial effects by helping to facilitate mechanical ventilation and prevent microasynchrony. Asynchrony can lead to alveolar collapse, and regional heterogeneity on alveolar structure. Increased alveolar pressures, as result of these changes in the lung architecture, can cause overdistention in non-dependent parts of the lung, thus improvement in microasynchrony allows patients the ability to tolerate optimal tidal volume and pressure settings to prevent these complications and permit appropriate lung recruitment [7,16]. By improving ventilator synchrony, NMBAs can also prevent ventilator-induced lung injury, by minimizing atelectrauma, barotrauma, and volutrauma, which can be pronounced during spontaneous breathing in ARDS patients [16].

1.2. Types of NMBAs

Only nondepolarizing NMBAs have been studied in the setting of ARDS as they provide a more prolonged neuromuscular blockade than depolarizing NMBAs [17]. Nondepolarizing NMBAs can further be classified as aminosteroid or benzylisoquinolinium compounds. The benzylisoquinoline, cisatracurium, is the only NMBA studied in the three trials published to date [7,18,19]. Cisatracurium is an isomer of atracurium, another benzylisoquinoline. Cisatracurium and atracurium may be preferred in critically ill patients as they undergo Hofmann elimination, which is a metabolic process which does not utilize an organ for metabolism and thus patients with renal or hepatic dysfunction do not require dose adjustments for use. Cisatracurium, and atracurium to a lesser degree, are both metabolized to the metabolite laudanosine which is primarily renally eliminated. Accumulation of laudanosine may result in hypotension and bradycardia. One other difference between cisatracurium and atracurium is the histamine release which occurs only with atracurium resulting in flushing, tachycardia, and hypotension [20-23]. Due to these differences between atracurium and cisatracurium, a single center, retrospective study evaluated these agents in an early (≤ 72 h of ARDS onset) severe ARDS patient population (PaO_2/FiO_2 ratio < 150 mmHg) to determine if these differences impact the effectiveness of these agents. This study found no difference in median improvement in the PaO_2/FiO_2 ratio at 72 h when comparing atracurium and cisatracurium (65 [25–162] mm Hg vs. 66 [16–147] mm Hg, $p = 0.65$). There was also no difference in intensive care unit (ICU) length of stay ($p = 0.34$) or in-hospital mortality ($p = 0.42$) [24]. Despite no differences in these clinical endpoints, this was a small, single center retrospective study and was unable to account for differences in other pharmacologic or nonpharmacologic treatment strategies. The greatest limitation of this study is that it did not evaluate adverse effects associated with atracurium and cisatracurium, particularly those effects associated with the metabolite, laudanosine, especially since patients with renal dysfunction were not excluded from the analysis, nor was baseline renal function reported. The efficacy information may be helpful, however, in times of drug shortages or in those institutions with cost constraints using cisatracurium.

In another recently published observational trial, patients with ARDS or at risk for ARDS who received a continuous infusion of cisatracurium or vecuronium for ≥2 days within 2 days of hospital admission were evaluated. This study did not find a difference in mortality (OR 0.93; $p = 0.40$) or length of hospital stay (0.66 days; $p = 0.41$) when propensity matching patients who received cisatracurium with patients who received vecuronium. However, patients who received cisatracurium did have a shorter duration of mechanical ventilation (1.01 days; $p = 0.005$), ICU length of stay (0.98 days; $p = 0.028$) and were more likely to be discharged home (OR 1.19; $p = 0.056$) [25]. These observed differences in clinical outcomes may be related to the differences in chemical structure and pharmacokinetic properties when comparing cisatracurium and vecuronium. Cisatracurium has a faster metabolic clearance rate than vecuronium due to its metabolism and elimination being independent of organ function. Therefore, prolonged neuromuscular blockade with vecuronium may have resulted in prolonged duration of mechanical ventilation and ICU length of stay. Additionally, cisatracurium, a benzylisoquinoline, may decrease the risk of ICU acquired weakness, compared to aminosteroids, like vecuronium [26]. This theory cannot be proven, however, since this study did not evaluate adverse effects related to NMBA use [25]. Given the results of this study and the known pharmacologic differences between vecuronium and cisatracurium, caution should be used when substituting a benzylisoquinoline NMBA with an aminosteroid NMBA. More detailed information comparing NMBAs can be found in Table 1.

1.3. Use of NMBAs in ARDS

There is currently limited data regarding the use of NMBAs in critically ill patients with ARDS (Table 2), although it is estimated that 30–40% of patients with ARDS are prescribed an NMBA [2,27]. In a recent survey of adult intensivists practicing in the United States (US), 94% of respondents reported prescribing either intermittent or continuous infusion NMBAs for patients with ARDS and 62.1% considered NMBAs to be their preferred rescue therapy [28]. The current guidelines for sustained neuromuscular blockade in critically ill patients recommend administering continuous infusion NMBAs to patients with ARDS with a PaO_2/FiO_2 ratio of <150 mmHg early in their ARDS course [29]. This variability in clinical practice when prescribing NMBAs for ARDS is likely a result of the limited data evaluating NMBAs in this patient population.

In a multicenter, prospective, randomized controlled trial, the effect of NMBAs on gas exchange in patients with ARDS was evaluated. This study included 56 patients meeting the American-European Consensus Conference (AECC) criteria [30] for ARDS with a PaO_2/FiO_2 ratio of <150 mmHg and were enrolled within 36 h of ARDS onset. Patients were randomized to receive a continuous infusion of cisatracurium beginning at a rate of 5 μg/kg/min or placebo for 48 h and all patients were managed with low-tidal volume ventilation. Patients randomized to receive NMBAs had a higher PaO_2/FiO_2 at 48, 96, and 120 h after randomization ($p = 0.021$) and PEEP also decreased over time compared to placebo ($p = 0.036$). Although not powered to detect a difference in mortality, there was a trend toward improved ICU mortality in patients who received an NMBA compared to placebo (46.4% vs. 71.4%, $p = 0.057$). There was also no increase in adverse effects, including pneumothorax, barotrauma, critical illness neuromyopathy and ventilator-associated pneumonia, associated with NMBA use compared to placebo [18]. The results of this study demonstrated that early NMBA use in patients with moderate-severe ARDS, results in improved oxygenation and potentially improved mortality.

To further investigate the beneficial effects of NMBAs in patients with ARDS, a multicenter, randomized controlled trial evaluated 36 patients meeting the AECC definition for ARDS with a PaO_2/FiO_2 ratio of ≤200 mmHg within 48 h of ARDS onset and sought to evaluate the anti-inflammatory effects of NMBAs. Patients were randomized to receive a continuous infusion of cisatracurium beginning at a rate of 5 μg/kg/min or placebo and all patients were managed according to a low-tidal volume ventilation protocol. Bronchoalveolar lavage (BAL) and blood samples were used to measure inflammatory markers. Compared to placebo, patients who received an NMBA, had decreased levels of interleukin (IL)-1β, IL-6 and IL-8 both in the BAL and blood samples at 48 h following randomization. There was no effect on tumor necrosis factor-α in either the BAL or blood samples. The use of NMBA therapy also resulted in a sustained improvement in the PaO_2/FiO_2 ratio over the 120 h study period ($p < 0.001$). Again, although not powered to detect differences in mortality there was a trend toward decreased mortality in patients who received an NMBA compared to placebo (27.8% vs.

Table 1
Comparison of neuromuscular blocking agents [42].

Neuromuscular blocking agent	Onset	Duration	Metabolism	Adverse effects	Studied in ARDS?
Benzylisoquinoliniums					
Atracurium	3–5 min	20–35 min	Hoffman elimination	Flushing, seizure (laudanosine), hypotension (histamine release), tachycardia, bradycardia	Single center, observational [24]
Cisatracurium	2–3 min	30–60 min	Hoffman elimination	Bronchospasm, bradycardia	Multicenter RCT [7]
Aminosteroids					
Pancuronium	2–3 min	60–100 min	Renal	Flushing, hypotension, tachycardia	No
Rocuronium	1–2 min	20–35 min	Hepatic	Tachycardia	No
Vecuronium	3–4 min	20–45 min	Hepatic; metabolites excreted renally	Bradycardia	Multicenter, observational [25]

RCT: randomized controlled trial.

55.6%, p = NS) and there were no differences in adverse effects, including critical illness neuromyopathy and barotrauma [19]. This study helped to corroborate one of the proposed mechanisms by which NMBA may exert their beneficial effects in patients with ARDS.

In the ACURASYS trial, the largest study currently published evaluating NMBAs in ARDS, 340 patients meeting the AECC criteria for ARDS with a PaO_2/FiO_2 ratio of <150 mmHg and were within 48 h of ARDS onset were randomized to receive either cisatracurium 37.5 mg/h or placebo for 48 h in addition to a lung protective ventilation strategy using low-tidal volume ventilation. The primary endpoint of this study was mortality at 90 days for which the hazard ratio was 0.68 (95% confidence interval [CI] 0.48–0.98, $p = 0.04$) after adjusting for the Simplified Acute Physiology II score and baseline PaO_2/FiO_2 ratio and plateau pressures. The crude 90-day mortality (31.6% vs. 40.7%, $p = 0.08$) and

Table 2
Studies evaluating NMBA use in ARDS.

	Gainnier et al. [18]	Forel et al. [19]	Papazian et al. [7]	Huang et al. [31]
Design	Prospective, multicenter, randomized, placebo-controlled design			
Patients	- 56 patients - ARDS (PaO_2/FiO_2 < 150 mmHg at PEEP ≥5 cm H_20) - Enrolled within 36 h	- 36 patients - ARDS (PaO_2/FiO_2 < 150 mmHg at PEEP ≥5 cm H_20) - Enrolled within 48 h	- 340 patients - ARDS (PaO_2/FiO_2 < 150 mmHg at PEEP ≥5 cm H_20) - Enrolled within 48 h	- Maximum enrollment 1408 patients - ARDS (PaO_2/FiO_2 < 150 mmHg at PEEP ≥8 cm H_20) - Enrolled within 48 h
Methods	- Cisatracurium 50 mg, then 5 μg/kg/min × 48 h titrated by protocol - Protocolized: - Deep sedation - Assist-control mode; TV 6–8 ml/kg IBW - Gas exchange variables over a 120 h period	- Cisatracurium 0.2 mg/kg, then 5 μg/kg/min × 48 h titrated by protocol - Protocolized: - Deep sedation - Assist-control mode; - TV 6–8 ml/kg IBW - BAL and blood samples at baseline and 48 h	- Cisatracurium 15 mg, then 37.5 mg/h × 48 h - Protocolized: - Deep sedation - Ventilation procedure	- Cisatracurium 15 mg, then 37.5 mg/h × 48 h - Protocolized: - Deep sedation - High PEEP/FiO_2 titration - Low TV - SBT - Recommendations: - Proning - Fluid management
Outcomes	Cisatracurium - Higher PaO_2/FiO_2 at 48, 96, and 120 h ($p = 0.021$) - Decreased PEEP ($p = 0.036$), peak pressures ($p = 0.001$), and plateau pressures ($p = 0.012$) - No difference in oxygenation after 1 h - ICU mortality - Cisatracurium 46.4% vs. control 71.4% ($p = 0.057$) Adverse effects - Pneumothorax ($n = 1$) in control group	Cisatracurium - Decreased BAL IL-8 ($p = 0.034$) and serum IL-6 (p = 0.05) and IL-8 ($p = 0.003$) at 48 h - TNFα unchanged in BAL and serum - Greater decrease in PEEP, FiO_2, peak and plateau pressures over time with cisatracurium - ICU mortality - Cisatracurium 27.8% vs. control 55.6% (p = ns) - No difference in adverse effects	- 90-day mortality - Cisatracurium 31.6% vs. control 40.7% ($p = 0.08$) - 28-day mortality - Cisatracurium 23.7% vs. control 33.3% (p = 0.05) - Cisatracurium - Greater ventilator free days - Greater days without organ failure - Greater ICU free days - Adverse effects - Pneumothorax: Cisatracurium 4.0% vs. control 11.7% (p = 0.01) - Barotrauma: Cisatracurium 5.1% vs. control 11.7% (p = 0.03) - No difference in ICU-acquired paresis	- 90-day all-cause mortality - ICU acquired weakness - IL-6 levels - Hospital mortality - Ventilator free days - Organ failure free days - Hospital/ICU free days - Long-term follow-up
Favors NMBAs?	Yes	Yes	Yes	Results pending

NMBA: neuromuscular blocking agent; ARDS: acute respiratory distress syndrome; PaO_2: partial pressure of arterial oxygen; FiO_2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; TV: tidal volume; IBW: ideal body weight; hr: hour; SBT: spontaneous breathing trial; ICU: intensive care unit; IL: interleukin; BAL: bronchoalveolar lavage; TNF: tumor necrosis factor.

28-day mortality (23.7% vs. 33.3%, $p = 0.05$) were not statistically significant, but trended toward favoring NMBA therapy. In addition to a mortality benefit, NMBA use was associated with greater ventilator-free days (10.6 ± 9.7 days vs. 8.5 ± 9.4 days, $p = 0.04$), days free of non-respiratory organ failure during the first 28 days (15.8 ± 9.9 days vs. 12.2 ± 11.1 days, $p = 0.01$), and more ICU free days during the first 90 days (47.7 ± 33.5 days vs. 39.5 ± 35.6 days, $p = 0.03$). Patients who received an NMBA also had less barotrauma (5.1% vs. 11.7%, $p = 0.03$) and pneumothorax (4.0% vs. 11.7%, p = 0.01). There were no differences in ICU-acquired paresis or other adverse effects. In a sub-group analysis of patients stratified by PaO_2/FiO_2 ratio, patients with more severe ARDS ($PaO_2/FiO_2 < 120$ mmHg) had a greater probability of survival at 90 days (30.8% vs. 44.6%, $p = 0.051$) [7]. This was a large, multicenter, randomized study which demonstrated that early NMBA use in patients with early, severe ARDS results in improved adjusted mortality and less lung injury. This trial, however, had several limitations including a lower than expected mortality rate and was thus, underpowered. Additionally, the difference in the crude mortality rate between groups was not actually statistically significant and other adjuvant therapies (ie. nitric oxide, corticosteroids) for ARDS were not controlled.

The Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial is currently ongoing and hopes to address some of the limitations of the ACURASYS trial and replicate some of the benefits noted in this trial to more safely recommend this therapy before exposing critically ill patients with ARDS to NMBAs. The ROSE trial is a multicenter, randomized controlled trial enrolling patients meeting the Berlin criteria for ARDS with a PaO_2/FiO_2 ratio < 150 mmHg within 48 h of ARDS onset. Patients are randomized to receive either cisatracurium 37.5 mg/h for 48 h or placebo and all patients will receive protocolized low tidal volume ventilation, weaning, and high PEEP strategy [31]. The critical care community hopes that the results of this trial will provide better insight into the use of NMBAs in patients with early, severe ARDS.

Based on the limited published data, the 2016 Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient make a weak recommendation due to moderate quality evidence, for the use of a continuous infusion of an NMBA in patients early in their course of ARDS with a PaO_2/FiO_2 ratio < 150 mmHg. Based on the published literature they determined that the number needed to treat for NMBAs in patients with early ARDS is 8, but believe that further investigation into whether these results can be extrapolated to other NMBAs other than cisatracurium, if the infusion duration of 48 h is most beneficial, and if there are adverse effects associated with short-term NMBA use in patients with ARDS [29]. The 2017 American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine guidelines for the management of ARDS do not comment on the use of NMBAs for ARDS [6].

1.4. Severity of ARDS

To date, the published literature evaluating the use of NMBAs in patients with ARDS has been limited to patients with a PaO_2/FiO_2 ratio < 150 mmHg and ARDS according to the AECC definition for ARDS [7,18,19]. The mortality benefit attributed to NMBA use has only been seen in patients with a PaO_2/FiO_2 ratio < 120 mmHg and ARDS according to the AECC ARDS definition [7]. According to the contemporary Berlin definition for ARDS, severe ARDS is defined as a PaO_2/FiO_2 ratio < 100 mmHg and moderate ARDS is defined as a PaO_2/FiO_2 ratio 100–200 mmHg [32]. The current literature suggests that NMBAs offer the greatest benefit in the most severe ARDS patients (PaO_2/FiO_2 ratio < 120 mmHg). Hopefully, the ROSE trial using the Berlin ARDS definition will further clarify disease severity conferring a benefit from NMBA use.

1.5. Dose, timing, and duration of NMBAs

To date, the only study demonstrating a mortality benefit with NMBA for ARDS administered cisatracurium as a continuous infusion at a set rate of 37.5 mg/h [7]. A criticism of this study is the high set rate of NMBA, potentially leading to overexposure and adverse effects. Train-of-four (TOF) monitoring is recommended by the guidelines in addition to clinical assessment to measure the response to NMBAs [29]. Prior to the ACURASYS trial, studies comparing titration of NMBA to clinical outcomes vs. TOF have had mixed results [33-35], but a study comparing titration to TOF 0/4 vs. 2/4 found that patients titrated to TOF 2/4 had less cisatracurium exposure and a decreased recovery time overall compared to those patients titrated to a greater depth of paralysis [36]. A recent study of 30 patients with ARDS compared patients who received cisatracurium titrated to TOF vs. their cisatracurium exposure had they been managed according to the protocol used in the ACURASYS trial. Although a small study, this trial found that patients receiving NMBA titrated to TOF received significantly less NMBA without impacting the quality of neuromuscular blockade [37]. Despite small studies evaluating the impact of NMBA titration on efficacy and safety, the available data suggests that titration rather than a high fixed rate of continuous NMBAs may result in decreased NMBA exposure thereby potentially decreasing patient harm and medication costs.

Due to the ability of NMBAs to decrease inflammation, improve oxygenation, improve lung recruitment, and facilitate ventilator synchrony, NMBAs offer the most benefit when used early, during the exudative phase of ARDS. As lungs progress into the fibrotic stage of ARDS, although not directly studied, mechanistically the beneficial effects of NMBAs are likely lost, only exposing patients to the harmful effects of NMBAs [12,14]. Prospective studies evaluating NMBAs for ARDS have only evaluated these therapies within 48 h of ARDS onset and there is currently no basis for recommending NMBAs beyond this time period for patients with ARDS [7,18,19,31]. A survey of US intensivists, found that the majority of respondents reserve continuous infusion NMBAs for patients within 48 h of severe ARDS onset and limit their duration to 48 h, but significant variability in practice existed, despite a lack of literature to support these varied practices [38].

1.6. Risks associated with NMBA use

Despite the potential benefits of NMBAs in patients with early ARDS, their use is not without risk. The use of NMBAs has been associated with postparalytic quadriparesis, myopathy, skin breakdown, venous thromboembolisms (VTE), corneal abrasions and prolonged recovery [29]. Critically ill patients are at a high risk for VTE and the immobility that results from the use of NMBAs, further increases their risk. Adequate mechanical and pharmacologic VTE prophylaxis should be provided to patients while receiving NMBAs unless contraindicated [39,40]. The use of NMBAs may result in corneal abrasions as these medications do not allow for a corneal reflex or complete closure of the eyelid, exposing the cornea to damage [41]. Patients receiving NMBAs should receive lubricating eye gel or drops and eyelid closure to prevent corneal damage [29].

The use of NMBAs in critically ill patients can be further complicated by drug interactions and alterations in pH and electrolytes. Corticosteroids, cyclosporine, furosemide, beta-blockers, calcium-channel blockers, aminoglycosides, tetracyclines, vancomycin, and clindamycin may prolong the effects of NMBAs. The interaction between these medications and NMBAs is thought to be a result of a reduction in acetylcholine release or reduction in receptor sensitivity to acetylcholine [42]. If NMBAs must be prescribed concurrently with the use of these medications, patients should be closely monitored for prolonged paralysis following discontinuation of the NMBA. Although not clearly understood, respiratory and metabolic acidosis may also prolong the effects of NMBAs. Finally, electrolyte disturbances can also impact the duration of action of NMBAs with hypercalcemia decreasing the neuromuscular blockade

and hypokalemia and hypomagnesaemia increasing the duration of neuromuscular blockade [42,43].

In patients with ARDS, the incidence of ICU acquired weakness varies significantly with reports ranging from 30 to 60% [44]. Risk factors for ICU acquired weakness include hyperglycemia, hypoalbuminemia, multi-organ failure, female gender, administration of corticosteroids, and prolonged durations of vasopressor support, mechanical ventilation, and ICU length of stay [45-47]. As patients with ARDS likely have many risk factors for ICU acquired weakness, it was believed that NMBAs further increase a patient's risk. More recent data, however, suggests that NMBAs may not be associated with ICU acquired weakness, when used for durations <48 h and when not used with corticosteroids [47-51]. If possible, aminosteroid NMBA compounds should be avoided due to their chemical structure, which makes them more likely to be associated with myopathies [26].

Additionally, when patients do not receive appropriate analgesia and sedation prior to receiving NMBAs, they have reported having anxiety, sleeplessness, and post-traumatic stress disorder, often further complicating prolonged hospital courses and discharge to long-term care facilities associated with ARDS [52-54]. Although not extensively studied, patients who have undergone therapeutic paralysis often recall negative experiences and up to 36% of patients report having recall from the time of paralysis [52,53]. These survey findings are potentially a result of inadequate analgesia and sedation during the time of paralysis. Surveys have previously reported a lack of understanding by prescribers of the absence of sedative and analgesic properties of NMBAs and a recent survey of prescribers found that there is a lack of knowledge regarding the duration of action of paralytics, thereby potentially undersedating a patient in which paralysis may still be wearing off [38,55]. Standard protocols for analgesia and sedation while patients receive NMBAs are likely inadequate. Providers should seek to achieve adequate analgesia and sedation prior to initiating a NMBA as these are more difficult to assess and titrate medications to effect once a patient has been paralyzed [53,56]. A Bispectral Index may help prescribers and nurses better assess a patient's level of consciousness to prevent periods of wakefulness during paralysis [57]. This information highlights that more education regarding the appropriate use of NMBAs in the ICU is warranted to ensure safe use of these agents in patients with ARDS.

In conclusion, data evaluating the use of NMBAs in patients with ARDS is limited. However, the available data suggests there is a beneficial effect when using NMBAs in patients with early, severe ARDS for 48 h. Patients should be carefully monitored while receiving NMBAs and only short durations of use should be prescribed to prevent further complications. Hopefully, the results of the upcoming ROSE trial will provide more information regarding the use of NMBAs in ARDS patients.

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