Use of neuromuscular blocking agents in acute respiratory distress syndrome

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ABSTRACT

Acute respiratory distress syndrome is the result of an acute inflammatory response of the lungs, causing severe hypoxemia. A variety of therapeutic modalities have been extensively studied, with only a few demonstrating improvement in survival. Specifically, mechanical ventilation with use of low tidal volumes, prone positioning, and treatment with neuromuscular blocking agents have proven beneficial. This article focuses on the utilization of neuromuscular blocking agents in this entity. In particular, we briefly review the mechanism of action of neuromuscular blockades, the latest published evidence supporting their use in acute respiratory distress syndrome, and current recommendations for their utilization in clinical practice.

KEYWORDS Acute respiratory distress syndrome; mechanical ventilation; neuromuscular blocking agents

Acute respiratory distress syndrome (ARDS) was described in 1967 by Dr. Ashbaugh and colleagues as an acute inflammatory response of the lungs with consequent hypoxemia.¹ In 2011, a panel of experts developed the Berlin definition, which defined ARDS as a syndrome occurring within 1 week of a known clinical insult or worsening respiratory symptoms, with evidence of bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules. The Berlin definition also divided ARDS into three categories based on the degree of hypoxemia but considering the level of positive end-expiratory pressure (PEEP; *Table 1*).¹ A landmark study comparing mechanical ventilation with lower tidal volumes (6 cc/kg of predicted body weight) vs traditional tidal volumes (12 cc/kg) showed a reduction in mortality by almost 9% and became the standard of care for the management of ARDS.² Many other therapeutic modalities have since been evaluated: high-frequency oscillatory ventilation,^{3,4} airway pressure release ventilation,⁵ inhaled vasodilators,⁶ and extracorporeal membrane oxygenation.^{7,8} Two strategies that have gained significant attention after demonstrating improvement in survival are prone positioning and use of neuromuscular blocking agents (NMBAs).⁹ Despite its positive effect, prone positioning remains underutilized in clinical practice, because it requires trained and experienced personnel to obtain desirable outcomes. Therefore, the use of continuous infusion of NMBAs may be seen as a valuable strategy in a group of patients with severe ARDS not responding to standard of care

Table 1. Classification of ARDS based on Berlin definition

Type	Description
Mild	$\text{PaO}_2/\text{FiO}_2$ 201–300 with PEEP or CPAP $\geq$ 5 cm H ₂ O
Moderate	$\text{PaO}_2/\text{FiO}_2$ 101–200 with PEEP $\geq$ 5 cm H ₂ O
Severe	$\text{PaO}_2/\text{FiO}_2 \leq$ 100 with PEEP $\geq$ 5 cm H ₂ O

ARDS indicates acute respiratory distress syndrome; CPAP, continuous positive airway pressure; $\text{PaO}_2/\text{FiO}_2$, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

therapy.¹⁰ This article reviews the mechanism of action of NMBAs, the evidence for their use in ARDS, and current recommendations.

MECHANISMS OF ACTION OF NMBAS

A neuromuscular junction is composed of a presynaptic motor axon that abuts acetylcholine receptors of skeletal muscle cells. Upon activation, the neuron releases acetylcholine, activating the skeletal muscle cell and thereby allowing the flow of sodium and potassium to trigger a muscle contraction.¹¹ NMBAs competitively bind to the acetylcholine receptor, preventing activation of the muscle cell by acetylcholine. NMBAs are classified as depolarizing or nondepolarizing agents. Depolarizing agents mimic the effect of acetylcholine at the neuromuscular junction, and these include succinylcholine

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and decamethonium. Normally, when acetylcholine binds to the acetylcholine receptor on muscle cells, the channel opens for a very short duration because acetylcholinesterase rapidly degrades the transmitter in the perijunctional area.¹² Conversely, depolarizing agents have a biphasic action, because they mimic acetylcholine by causing muscle contractions and, subsequently, they cause paralysis due to decreased susceptibility to degradation by acetylcholinesterase. Nondepolarizing NMBA are also competitive antagonists at the nicotinic acetylcholine receptor but differ from depolarizing agents because they bind for longer periods of time, preventing acetylcholine from binding.¹³ Importantly, these agents are lipophobic, so they do not cross the blood-brain barrier. Among nondepolarizing agents, pancuronium, cisatracurium, and atracurium have all been studied in the ARDS population. Atracurium was developed in 1981 by Stenlake and colleagues.¹⁴ It is a benzylisoquinoline molecule that breaks down irreversibly at physiological pH and temperature based on the principles of Hofmann elimination.¹⁵ This characteristic presents important advantages in critically ill subjects, allowing its utilization in patients with kidney, liver, or multiorgan failure.¹⁶ However, atracurium may cause histamine release with consequent cardiovascular effects, hypotension, cutaneous flushing, and tachycardia. These effects are usually reversible within 5 minutes postadministration. As previously stated, atracurium undergoes Hofmann elimination; one of the metabolites associated with this elimination path is laudanosine, which has been reported to cross the blood-brain barrier and decrease the seizure threshold. Nevertheless, multiple studies demonstrated that concentrations of laudanosine needed to trigger seizures are much higher than those generated by doses of atracurium used in clinical practice.¹⁷ Cisatracurium is an optical isomer of atracurium and is slightly more potent. It also undergoes Hoffman elimination. Because cisatracurium causes less histamine release and concentrations of laudanosine are reportedly lower compared with atracurium, this NMBA presents hypothetical advantages.¹⁸

EVIDENCE OF NMBA USE IN ARDS

The first NMBA reported as a potential treatment for ARDS was pancuronium. Specifically, a report from 1975 described the use of pancuronium in 6 patients with ARDS with a goal to improve patient-ventilator synchrony.¹⁹ Later, in 1984, Bishop reported the use of a single bolus of pancuronium in 9 patients with acute lung injury/ARDS.²⁰ Nevertheless, no hemodynamic or oxygenation effects were seen in those patients.²⁰ Interestingly, a survey sent out in 1990 showed that paralytics were already being utilized for ARDS without extensive research to support their benefits.²¹ Major studies that have evaluated NMBA in ARDS have been conducted since these early reports. The first prospective randomized control study, which included the use of cisatracurium as an infusion for a period of 2 hours, included 102 patients with ARDS. These patients were randomized to two different levels of paralysis based on train-of-four (TOF) monitoring. No placebo group was included. The study showed improvement of

oxygenation and plateau pressures in both groups, showing no differences when aiming for TOF of 0 of 4 or 2 of 4.¹¹ Another multicenter prospective randomized controlled study, published in 2004, included 56 patients with a partial pressure of arterial oxygen and fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio <150 and PEEP ≥ 5 cm H_2O . Neuromuscular blockade for 48 hours was utilized vs placebo and resulted in significant improvement in oxygenation, manifested by a higher $\text{PaO}_2/\text{FiO}_2$ ratio at 48, 96, and 120 hours postrandomization. Furthermore, the level of PEEP required to achieve similar oxygenation compared with the placebo group was reduced.²² In this study, the proposed mechanism for the improvement in oxygenation was a reduction in proinflammatory cytokines, leading to a decrease in lung permeability and inflammatory response. In a follow-up study published in 2006, Forel and colleagues²³ reviewed the effects of NMBA on pulmonary and systemic inflammation. The study involved collection of blood samples and bronchoalveolar lavages upon admission with ARDS and 48 hours after NMBA treatment vs control. The authors investigated concentrations of tumor necrosis factor-alpha, interleukin (IL)-1beta, IL-6, and IL-8. Notably, the study found that after 48 hours, pulmonary concentrations of IL-1beta, IL-6, and IL-8 were lower in the neuromuscular blockade group vs the control group. There was a serum decrease in IL-6 and IL-8 as well. Furthermore, this trial confirmed a sustained improvement in the $\text{PaO}_2/\text{FiO}_2$ ratio with NMBA utilization.²³

Based on the previously described experiences, Papazian and colleagues investigated the use of NMBA and their effect in clinical outcomes.¹⁰ Specifically, patients with severe ARDS, defined as $\text{PaO}_2/\text{FiO}_2$ ratios <150 , were randomized to a continuous infusion of cisatracurium vs placebo. Interestingly, the authors found that treatment with cisatracurium for 48 hours improved the adjusted 90-day survival rate with a hazard ratio of cisatracurium compared with placebo of 0.68 ($P = 0.04$). Furthermore, the cisatracurium group had a higher number of ventilator-free days at 90 days (hazard ratio of 1.41; $P = 0.01$) and organ failure-free days at 28 days (15.8 days vs 12.2 days in the cisatracurium group vs placebo group, respectively; $P = 0.01$). Notably, the incidence of intensive care unit (ICU)-acquired paresis at 28 days or upon ICU discharge was not statistically different between groups.¹¹ A recently published retrospective study compared a continuous infusion of atracurium vs cisatracurium in patients with severe ARDS. There was no difference in oxygenation improvement at 72 hours post-NMBA initiation. Furthermore, ventilator-free days at 28 days, ICU length of stay, and hospital mortality were not different among NMBA studied.²⁴

There is currently an open clinical trial to reevaluate systemic early NMBA with cisatracurium in a randomized, parallel assignment.²⁵ In addition, there is a second trial evaluating the effects of NMBA on the alteration of transpulmonary pressures in early phase ARDS.²⁶ The result of these trials may provide further evidence for their clinical utilization.

CLINICAL USE AND MONITORING

Given the findings of the previously described trials, the surviving sepsis campaign guidelines recommend a short course

of neuromuscular blockade for not longer than 48 hours in patients with early sepsis-induced ARDS and $\text{PaO}_2/\text{FiO}_2 < 150$ mm Hg.²⁷ Monitoring should include both clinical acumen and TOF. TOF should be titrated aiming at 1 to 2 twitches out of 4 applied stimuli, which equates to approximately 80% to 90% of blocked receptors.²⁸ The current guidelines make no recommendations regarding use of electroencephalogram-derived parameters as a measure of sedation but recommend using clinical judgment to monitor sedation.²⁹ In the paralyzed patient, common scales (i.e., the Richmond Agitation and Sedation Scale) are not useful to monitor sedation. Therefore, some institutions still use the Bispectral Index or the Patient State Index to determine levels of sedation in ICU patients. In terms of side effects, studies have not shown an increased risk of ICU-acquired weakness if NMBA are used for 48 hours.²⁹ However, current guidelines recommend a structured physiotherapy regimen.²⁹ Though atracurium may cause histamine release, hypersensitivity reactions are not frequently reported. There are no specific contraindications for NMBA use.

In summary, NMBA became a practical and evidence-based therapy in subjects with severe ARDS not responding to conventional ventilator strategies. Proper selection of blocking agents, as well as training in their use, monitoring, and expected complications, is fundamental to achieve desirable outcomes in this group of patients with already high mortality rates.

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