Neuromuscular blocker agents in mechanically ventilated patients with ARDS

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Abstract

The clinical use of neuromuscular blocker agents (NMBAs) in patients with moderate-to-severe acute respiratory distress syndrome (ARDS) is a controversial topic in critical care medicine. Of the two classes of NMBAs, the most widely used are the non-depolarizing agents including cisatracurium. Some of the benefits attributed to this class of medications for patients with ARDS include a decreased inflammatory response, prevention of ventilator dyssynchrony, and improved oxygenation. The mortality benefit of this intervention was recently studied by two main trials, ACURASYS and ROSE, which showed improved patient outcomes, but no mortality benefit was obtained. The decision to use NMBAs in the clinical practice has to be made in a case-by-case basis taking in consideration different scenarios.

Keywords: Mechanical ventilation, acute respiratory distress syndrome, neuromuscular blocking drugs, cis atracurium

Introduction

Curare, a lethal poison originally used by primitive hunters in the Amazon, was first introduced as the "flying death" by the Spanish conquistadors in the early 1500s upon returning from their expeditions to South America.[1] Centuries of research on this topic have led to the development of the paralytic agents that are used today.[1] Currently, the interest in neuromuscular blockade agents (NMBAs) focuses on patients on mechanical ventilation, particularly patients with acute respiratory distress syndrome (ARDS). These drugs are divided into 2 classes: depolarizing and non-depolarizing agents.[2]

Depolarizing drugs bind to acetylcholine (ACh) receptors, generating a muscle action potential. This class of NBMAs is not metabolized by acetylcholinesterase, allowing for a prolonged depolarization of the motor endplate and subsequent inactivation of the sodium channels that leads to paralysis.[2] In contrast, non-depolarizing agents do not stimulate the ACh receptors, and, therefore, no action potential is generated. This class of NBMAs functions as competitive antagonists at the ACh receptors.[2]

Although the use of NBMAs in mechanically ventilated patients remains controversial, non-depolarizing agents are the most widely used for this purpose. The clinical application of pancuronium, cisatracurium, and atracurium has been widely studied in patients with ARDS.[3] Two randomized controlled trials, ACURASYS and ROSE trials, have studied the benefits in patients' outcomes when using NMBAs in the early management of ARDS.

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Effects of NMBAs in ARDS

The evidence that supports the early use of NMBAs in severe ARDS is based on three benefits: improved oxygenation, decreased inflammatory response, and improved outcomes.[4–6] The proposed mechanisms to explain these effects associated with NBMAs include

a reduction in ventilator dyssynchrony, decreased respiratory demand, less atelectrauma, and reduced inflammation from direct anti-inflammatory effects of cisatracurium.[5]

In a study by Manthous et al., oxygen consumption in sedated patients on assist-control (AC) ventilation undergoing resuscitation after cardiopulmonary arrest was compared to that of the same patients after their mode of ventilation was changed to continuous positive airway pressure (CPAP).[7] In order to measure the oxygen cost of breathing, the authors measured oxygen consumption on AC ventilation after NMBAs were started. Their findings suggest that patients on AC ventilation, paralyzed with pancuronium, had an average of 18% reduction in oxygen consumption when compared to patients with spontaneous breathing on CPAP.[7] These findings have previously been demonstrated in canine models in which the data suggest that in hypoperfused states, spontaneous breathing leads to increased blood flow and increased oxygen consumption by the diaphragm, which in turn compromises the delivery of oxygen to other vital organs.[8]

Another focus of interest in this topic has been the inflammatory and mechanical injury inflicted in ARDS patients. The ARMA study demonstrated that low tidal volume ventilation (LTVV) reduced mortality and increased the number of days off the ventilator in patients with ARDS. However, it has been postulated that LTVV alone does not eliminate the development of ventilator-induced lung injury (VILI).[9] In a secondary analysis of the ARMA study, patients with severe ARDS (defined as: P/F less than or equal to 120 mmHg) treated with NMBAs and LTVV had decreased biomarkers of epithelial injury (surfactant Protein-D [SP-D]), endothelial injury (von Willebrand factor [VWF]), and systemic inflammation (IL-8).[9] These findings suggest that the improvement in patient outcomes with NMBAs and LTVV in severe ARDS is not only due to anti-inflammatory effects, but also due to reduced epithelial and endothelial injury.[9]

Four other studies have reinforced the idea that the early use of NMBAs in ARDS is associated with decreased inflammation. In a randomized controlled trial by Forel et al., pulmonary concentrations of tumor necrosis-alpha, IL-1 beta, IL-6, and IL-8 were compared between patients treated with lung-protective strategy ventilation plus NMBA and the control group (lung-protective strategy ventilation and placebo).[5] They found that at 48 hr of randomization, IL-1 beta, IL-6, and IL-8 were lower in the NMBA group compared to the control group.[5] In addition, an increase in the PaO_2/FiO_2 ratio was observed in the NMBA group.

It is important to remember that a challenge associated with the implementation of the LTVV approach in ARDS management is that the restriction in tidal volume (TV) often results in ventilator dyssynchrony or breath stacking dyssynchrony (BSD) which can lead to an increased TV and higher alveolar pressures.[10] Although different approaches have been studied to prevent BSD, it has been proposed that NMBAs improve ARDS survival by preventing BSD-mediated lung injury.

This theory has been further investigated by Beitler et al. in a study evaluating the performance of a new criterion to quantify BSD.[11] Thirty-three adult patients with ARDS requiring mechanical ventilation initiated within 24 hours were enrolled in this study. Only ten patients received NMBAs, seven of whom received cisatracurium, while three received rocuronium. The frequency of breath stacking dyssynchrony during NMBAs infusion was 0 breaths per hour, BSD minute-volume was 0.0 mL/kg/min, and no spontaneous breaths occurred during 88% of the time recorded under NBMA infusion.[11]

The mortality benefit of NMBAs has also been studied. To date, there are two main trials published in the last decade: the ARDS et Curarisation Systematiq (ACURASYS) trial published in 2010 followed by the Reevaluation Of Systemic Early Neuromuscular Blockade (ROSE) trial, published in 2019.

ACURASYS TRIAL

In the ACURASYS trial by Papazian et al., the 90-day mortality in patients with severe ARDS was studied.[6] The inclusion criteria included patients who presented to the intensive care unit (ICU) within 48 hours of acute respiratory failure requiring mechanical ventilation.

Patients were enrolled if their PaO_2/FIO_2 was less than 150 mmHg, they required a PEEP of 5 cm of water or higher, had the ventilator set to deliver a tidal volume of 6–8 ml/kg of predicted body weight, and had bilateral pulmonary infiltrates consistent with edema in the absence of left atrial hypertension. A total of 340 patients underwent randomization to receive placebo (n = 162) or cisatracurium (n = 178, one withdrew consent) for 48 hours.

Patients in the cisatracurium group received a 15 mg intravenous (IV) infusion followed by a continuous infusion of 37.5 mg/hr for 48 hours. The primary outcome in this study was 90-day mortality. Secondary outcomes included 28-day mortality, number of days outside the ICU, number of days without organ or system failure, rate of barotrauma, rate of ICU-acquired paresis, and number of ventilator-free days. Early administration of NMBAs in patients with moderate to severe ARDS resulted in an adjusted 90-day mortality benefit of 9.1%. The improved survival rate might be attributed to different reasons as these patients were also found to have increased number of ventilator-free days and days outside the ICU and decreased incidence of barotrauma in the first 90 days.

ROSE trial

In 2019 the ROSE trial, a multicenter, unblinded, randomized trial that included patients with moderate to severe ARDS, was published.[12] The trial's goal was to evaluate the efficacy and safety of early neuromuscular blockade (15 mg IV infusion followed by a continuous infusion of 37.5 mg/hr for 48 hours) and concurrent heavy sedation compared to a lighter sedation approach and no neuromuscular blockade.

Patients were enrolled if they were on mechanical ventilation with PaO_2/FIO_2 less than 150 mmHg, with a PEEP of 8 cm or more of water, bilateral pulmonary opacities on chest imaging, and respiratory failure not explained by cardiogenic causes or fluid overload. A total of 1,008 patients underwent randomization (502 assigned to an intervention group, 506 assigned to a control group.) The primary end point was in-hospital death from any cause at 90 days. Secondary end points included organ dysfunction, in-hospital death, days out of the ICU, and days free of mechanical ventilation. The study's results concluded that for the primary and secondary end point results no significant improvement in mortality at 90 and 28 days occurred. However, the intervention group had lower PEEP and FiO_2 requirements, lower minute ventilation, and higher driving pressures than the control group. In terms of adverse effects, more cardiovascular events were reported in the intervention group, and there was no difference in rates of pneumothorax and barotrauma between groups (ROSE).

Recent meta-analyses

More recently, 2 meta-analysis of randomized controlled trials (RCTs) with NBMAs in patient with ARDS have investigated the mortality differences in patients who received NBMAs vs patients who received placebo or conventional treatment.

In 2020, a meta-analysis by Ho et al. included 5 RCTs with patients who were randomized to receive NBMAs within 48h of a moderate to severe ARDS diagnosis. A total of 1462 patients participated in the 5 trials, and different parameters, including mortality, ventilator days and adverse events were studied. In terms of mortality, the cisatracurium group did not have reduced mortality at 28 and 90 days; however, the intervention group had a lower ICU mortality rate compared to the control group.[14] When the duration of mechanical ventilation and ventilator-free days were compared, no difference between the cisatracurium group and the control group were noted.[14] The cisatracurium group had a statistically significant lower risk for barotrauma, but there was no difference in risk for ICU-related weakness between the two groups. In addition, there was no difference in plateau pressures between the NBMA group and the control group. The PaO_2/FiO_2 ratio was higher at 48 hours and at 72 hours in the intervention group.[14]

In 2021, a similar meta-analysis comparing outcomes among ARDS patients who received NBMAs vs placebo was published. In this study by Torbic et al., six RCTs were included with a total of 1558 subjects.

The authors concluded that there was a decreased risk of mortality at day 21–28, and a decreased risk of ICU mortality in subjects with early ARDS who received a continuous NBMA infusion; there was no improvement in 90-day mortality.[15] This study also identified a reduced incidence of barotrauma and pneumothorax in the intervention group as compared to placebo, and there was no increased risk in ICU-related weakness. Patients who received NBMAs had an improvement in the PaO_2/FiO_2 ratios at 48 and 72 hours after randomization, but not within the first 24 hours. In this meta-analysis, the early use of NMBAs did not result in a decreased number of ventilator-free days, improvements in plateau pressures, or the use of higher PEEP.[15]

Discussion

The benefits of NMBAs are well documented. Although there is not a consensus in mortality benefit with the early use of paralytic use in moderate to severe ARDS, the use of these agents can offer some advantages in a select patient population. Presently the use of NMBAs for ARDS in current guidelines is weak.[13] However, it is important for a clinician to recognize when the use of NMBAs might be beneficial in particular scenarios.

Some of the benefits of implementing NMBAs in a case by case basis include improved oxygenation, decreased inflammatory response, and reduced epithelial and endothelial injury. Patients who could also benefit the most are those who exhibit signs of ventilator dyssynchrony despite appropriate sedation and analgesia.

The ACCURASYS trial demonstrated that the early use of cisatracurium can reduce barotrauma and the number of days on the ventilator, which can lead to fewer ICU days. The ROSE trial has provided data that suggest the use of NMBAs leads to less PEEP, FIO_2 requirements, and lower minute ventilation, which can lead to fewer days on a ventilator. When using these drugs in practice, it is important to remember some of the adverse effects that have been identified in the ACURASYS and ROSE trials, including increased risk for cardiovascular events[12] and myopathy[6] that might prolong a patient's recovery.

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