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Effects of the use of neuromuscular blocking agents on acute respiratory distress syndrome outcomes: A systematic review

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ABSTRACT

Background and purpose: Acute respiratory distress syndrome (ARDS) is a high-mortality disease with limited treatment options. Optimization of gas exchange while limiting damage to the lungs is key. The use of neuromuscular blocking agents may limit hypoxemia while preventing ventilator-induced lung injury.

Methods: A literature search was conducted using Ovid Medline and the exploded MeSH terms ARDS, acute respiratory distress syndrome, neuromuscular blockade, neuromuscular blocking agents, and paralytics. With limitations applied, three original randomized controlled trials investigating the use of neuromuscular blocking agents (NMBAs) in severe ARDS were identified and reviewed.

Conclusions: Two of the three trials demonstrated improved primary outcomes with the use of NMBA. The third trial was underpowered (due to unanticipated low mortality in the control group) and did not show a statistically significant improvement in the primary outcome. As all the original research was conducted by the same group, further investigation is necessary to assess generalizability and confirm results. Currently, additional research is underway, focusing on early enrollment and narrow inclusion criteria.

Implications for practice: Secondary analysis from two separate groups concluded the improved outcomes, with no evidence of increased risk of critical illness polyneuropathy or myopathy, suggest that the use of NMBAs in severe ARDS is appropriate.

Keywords: Acute respiratory distress syndrome; neuromuscular blockade; neuromuscular blocking agents; paralytics.

Journal of the American Association of Nurse Practitioners 30 (2018) 327–332,

DOI# 10.1097/JXX.0000000000000047

Acute respiratory distress syndrome (ARDS) is a high-mortality disease (40%) that can result from a variety of critical illnesses, such as trauma, abdominal surgery, sepsis, influenza, and pneumonia (Piantadosi & Schwartz, 2004). Although the inpatient management of ARDS is reserved for practitioners in the critical care environment, patients of all ages and walks of life can be affected by ARDS and the sequelae of treatment. Practitioners across the health care spectrum see patients who go on to develop ARDS or who are on the path to recovery after survival.

Acute respiratory distress syndrome is characterized by lung inflammation leading to reduced compliance and potentially severely limited gas exchange and hypoxemia. Management of hypoxemia becomes central to management and survival of ARDS. In recent years, significant steps have been made to identify strategies that reduce hypoxemia and mortality, including low-tidal-volume ventilation (LTVV), high positive end-expiratory pressures (PEEPs), prone positioning, and neuromuscular blockade (Bein et al., 2016). The role of neuromuscular blocking agents (NMBAs) as an adjuvant therapy in refractory ARDS is disputed. This article will review the historical milestones of ARDS management and progress to the most current primary research in the field. The goal was to identify best practice by analyzing outcomes of patients with ARDS comparing those treated with NMBAs versus those not treated with NMBAs.

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Received: *10 January 2018; revised 15 February 2018; accepted 20 February 2018*

Background

The necessity of ventilators to support gas exchange during ARDS is widely speculated as putting patients at risk for worsening intraparenchymal inflammation through ventilator-induced lung injury (VILI) (The Acute Respiratory Distress Syndrome Network [ARDSNET], 2000). Therefore, research has been geared toward interventions to reduce VILI. The LTVV strategy first introduced

by Amato et al. (1998) has led to the most significant improvement in mortality through the decreased lung trauma via the use of conservative tidal volumes and has since become the standard of care for ARDS management (Bein et al., 2016).

The first significant change followed the landmark paper by Amato et al. (1998), which demonstrated improved mortality in patients receiving tidal volumes of 6 mL/kg predicted body weight (PBW) versus 12 mL/kg PBW ($p < .001$). Following this revelation, further investigation has taken place in ways to optimize mechanical ventilation while not further damaging inflamed and fragile lung tissue (Neto, Pereira, Espósito, Damasceno, & Schultz, 2012). Additional research into other strategies that may reduce the stress of mechanical ventilation on the lung parenchyma include high PEEP ventilation strategies, prone positioning, ventilator titration based on plateau pressures, and reduction of driving pressures (Slutsky & Ranieri, 2013).

Low-tidal-volume ventilation

Low-tidal-volume ventilation is one of two well-established and widely accepted aspects of lung-protective ventilation (Bellani, Laffey, Pham, & Fan, 2016). The study of LTVV was the first big success of the ARDSnet group. Prior to the study by Amato et al., 1998, common tidal volumes were 10–12 mL/kg PBW. The large, multicenter trial showed improved mortality with 6 mL/kg PBW tidal volumes (versus 12 mL/kg PBW) ($p = .007$), so much so that the trial was ended early because of improved outcomes in the treatment group (Amato et al., 2000). At this point, only 6 mL/kg PBW tidal volumes versus 12 mL/kg PBW tidal volumes have been studied. Currently, there are no data examining slightly higher or lower than 6 mL/kg PBW tidal volumes.

Current practice standards recommend tidal volumes of 6 mL/kg PBW (Bein et al., 2016). However, it should be considered in patients with larger areas of nonaerated lung; even lower tidal volumes may be necessary to prevent overdistension (Brower et al., 2006). Previously, the mechanism of benefit from small tidal volumes was thought to be reduced volutrauma (injury from overdistension of the alveoli from high volumes) and barotrauma (injury from high pressures experienced by the alveoli, which can lead to rupture and pneumothorax); evidence now supports that low tidal volumes attenuate pro-inflammatory mediators, IL-6 and IL-8 and possibly others, associated with adverse clinical outcomes (Forel et al., 2006; Parsons et al., 2005).

High positive end-expiratory pressure. The second foundation of lung-protective ventilation is high PEEP. Unlike LTVV, this component of lung-protective ventilation tends to be reserved for patients with established ARDS as high PEEP increases intrathoracic pressure and can compromise cardiac filling pressures and uninjured lungs can potentially suffer over distension (Briel et al., 2010). High PEEP was introduced as a treatment strategy by the ARDSnet group in 2004; however, the initial data were equivocal (Brower et al., 2004). In 2006, Villar et al. repeated the trial with a more robust design around control of other variables and demonstrated that high PEEP strategies were associated with improved intensive care unit (ICU) and hospital mortalities ($p = .040$ and .041, respectively) (Villar, Kacmarek, Perez-Mendez & Aguirre-Jaime, 2006). However, the control group in this study also had higher tidal volumes, at 9–11 mL/kg PBW versus 5–8 mL/kg PBW in the intervention group. Several other studies on high PEEP have been conducted, and in 2010, a systematic review and meta-analysis by Briel et al found that high PEEP is associated with improved hospital survival in patients with ARDS and a P:F ratio of <200 (Briel et al., 2010). However, the studies evaluated in that review were very heterogeneous, and titration of PEEP was based at times on oxygenation and at times on airway pressures. At this point, further study is necessary to determine optimum PEEP levels and the measure by which to titrate.

Prone positioning

Placing patients with refractory hypoxemia in the prone position has been well established to improve oxygenation (Piedaleu & Albert, 2003). The presumed mechanisms included increased end-expiratory lung volume (lung recruitment), improved ventilation–perfusion matching, reduced lung compression by the weight of the heart, and increased homogeneity of ventilatory volume distribution (Slutsky & Ranieri, 2013). However, before 2013, there were data lacking to show improved mortality with the use of prone positioning. In 2006, a multicenter trial of prone positioning demonstrated improved oxygenation, but no clear improvement in mortality (Mancebo et al., 2006). However, in 2013, the intervention gained more attention following the landmark study by the PROSEVA group, who demonstrated a 50% reduction in mortality in the prone group ($p < .001$) (Guerin et al., 2013). The study has since been criticized due to the heterogeneity between the control and intervention groups. The control group was sicker and received less use of NMBA, suggesting that the effect may not be as significant as reported. Of interest, in the PROSEVA study, the magnitude of improvement of oxygenation did not correlate to survival. This suggests that the beneficial effects of proning are not limited to immediate, observable improvement in oxygenation but carry over to other, less readily observable physiologic benefits as well (Guerin et al., 2013).

Use of neuromuscular blocking agents

Paralysis with NMBAs is another strategy with several possible mechanisms for reducing VILI. By preventing ventilator dyssynchrony through paralysis, NMBAs

prevent volutrauma and barotrauma (Slutsky, 2010). By eliminating native expiratory work, NMBAs may allow for better maintenance of higher PEEP, reducing atelectrauma (injury from repeated opening and closing of alveoli) (Slutsky, 2010). Additionally, reducing the various types of VILI likely causes a reduction in inflammatory mediators, which are thought to perpetuate lung injury and worsen ARDS (Bein et al., 2016). Neuromuscular blocking agents also likely reduce oxygen consumption as the energy expenditure of the skeletal and respiratory muscles is diminished (Slutsky, 2010).

The use of NMBAs in refractory hypoxemia was introduced in the literature in 1991, when a survey of 265 hospitals revealed that 98% used NMBAs for acute respiratory failure, but only in 20% of cases (Hansen-Flaschen, Brazinsky, Basile, & Lanken, 1991). The use of NMBAs has since grown in popularity. However, unlike the above-described interventions, NMBA use in ARDS has limited data supporting the practice. The following analysis considers the empirical evidence on the use of NMBAs in management of ARDS.

Methods

A systematic literature review was performed to identify empirical evidence supporting or opposing the use of NMBAs in ARDS. The search was conducted using Ovid Medline exploding the MeSH terms ARDS, acute respiratory distress syndrome, neuromuscular blockade, neuromuscular blocking agents, and paralytics. Inclusion criteria were original randomized controlled trials (RCTs), English language, peer reviewed, adult human subjects, and published within the last 5 years. These criteria resulted in zero studies, so the time frame was expanded to 10 years, which resulted in one trial. Further liberalization to 20 years yielded an additional two studies. For ease of identification, the reviewed RCTs will be marked with an asterisk (*) hereafter in the text.

Results

All three trials identified in the literature search came from the same working group of authors, conducting ARDS research in France. They are a well-renowned group who have been involved in most of the major ARDS research over the last 20 years. The following is an evaluation of the presented data from these three trials. See Table 1 for a summary of findings.

The first pilot study of NMBAs in ARDS came about because NMBAs were widely being used in the management of ARDS, but the practice was controversial and efficacy largely anecdotal (Gainnier et al., 2004). Some argued that NMBAs actually worsened outcomes by further deteriorating ventilation perfusion mismatch, increasing risk of infection, and causing long-term neuromuscular damage (Rehder, Sessler, & Rodarte, 1977). To address the controversy, a single-institution, open prospective randomized controlled study enrolled 56 patients from four ICUs (Gainnier et al., 2004). Patients were randomized to either the treatment arm, which received a bolus dose of cisatracurium followed by a continuous infusion for 48 hours, or the placebo arm. The primary outcome measure was oxygenation over 120 hours as measured by the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2 ratio). Data analysis showed beneficial effects on PaO_2/FiO_2 ratio at 48, 96, and 120 hours (p values .014, .023, and .02, respectively). Statistically significant changes in PEEP and plateau pressure were noted between the two groups. The mechanism by which the use of NMBAs may improve oxygenation is unknown, but some theories are that paralysis may reduce oxygen consumption and/or enhance chest wall compliance. Through skeletal muscle paralysis, NMBAs inherently remove ventilator dyssynchrony, allowing for compliance with low-tidal-volume settings. Based on the outcome of this pilot study, the authors recommended further study to consider whether NMBAs improve outcomes in ARDS (Gainnier et al., 2004).

The second published study on the use of NMBAs in ARDS focused on assessment of inflammatory mediators rather than oxygenation (Forel et al., 2006). The primary outcome was the measurement of tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β, IL-6, and IL-8 in bronchoalveolar lavage and plasma samples. The secondary outcome was PaO_2/FiO_2 ratio. The authors report a decrease in the presence of the inflammatory mediators TNF-α, 1β, IL-6, and IL-8 and improvement in the PaO_2/FiO_2 ratio, supporting the findings of the pilot study by Gainnier et al. (2004).

The most recent study on the use of NMBAs for ARDS is known as the ACURASYS trial. ACURASYS considered whether cisatracurium improved survival at 90 days compared with placebo in early, severe ARDS (Papazian et al., 2010). This study was larger than the previous two studies (n = 340 versus n = 56 and n = 36, respectively), and the authors found improvement in many of the secondary outcomes, including 28-day mortality, organ failure–free days, ventilator-free days, ICU-free days. Additionally, rates of barotrauma and pneumothorax were both significantly reduced. However, the primary outcome, 90-day mortality, did not have a significant improvement at 95% confidence intervals (31.6% for the cisatracurium group vs. 40.7% for the placebo, p = .08). The authors suggest that the study was underpowered, as the placebo group had a lower mortality than they predicted (40% vs. 50%), based on previous studies. When they refocused their data analysis on only patients with a PaO_2/FiO_2 ratio of <120, a significant improvement in the cisatracurium group compared with the placebo group was found, leading them to suggest that the benefit may be isolated to patients with more severe ARDS (Papazian et al., 2010).

Table 1. Summation of results by study group

Study	Gannier et al. (2004)	Forel et al. (2006)	Papazian et al. (2010)
Primary outcome	PaO_2/FiO_2 ratio; $p = .21$	TNF-α, IL-1β, IL-6, and IL-8 (BAL and plasma) BAL $p = .034$ (IL-8 only) Plasma $p = .05$ (IL-6) and $p = .003$ (IL-8)	90-day mortality, $p = .08$
Secondary outcomes			
PaO_2/FiO_2 ratio	—	$p = .13$ to $p = .002$ (over 48–120 hours)	$p = .03$
28-day mortality	$p = .061$	—	$p = .05$
60-day mortality	$p = .18$	—	—
Ventilator-free days (at day 28)	$p = .24$	NS	$p = .04$
ICU mortality	$p = .057$	NS	$p = .06$
N	56	36	340
Limitations?	Small *n*	Small *n*	Underpowered

Note: BAL = broncho-alveolar lavage; ICU = intensive care unit; IL = interleukin; NS = not significant; PaO_2/FiO_2 ratio = partial pressure of arterial oxygen to fraction of inspired oxygen ratio; PEEP = positive end-expiratory pressure; Pplat = plateau pressure; TNF-α = tumor necrosis factor alpha.

Study limitations

Tidal volumes. Consideration of the above studies yields several points that require consideration. First, all three studies spoke to using LTVV strategies as indicated by the landmark ARDSNET study (2000). ARDSNET demonstrated that 6 mL/kg ideal body weight (IBW) tidal volumes were associated with lower mortality than 12 mL/kg IBW tidal volumes, which had been common practice until that time. Although the reviewed studies treated patients with "low-tidal-volume strategies," actual tidal volumes used were consistently greater than 6 mL/kg: 7–7.5 mL/kg IBW (Gainnier et al., 2004); 6.5–7.3 (Forel et al., 2006); and 6.48–6.55 (Papazian et al., 2010). At the time of these NMBA studies, there had been no RCTs narrowing optimum tidal volumes beyond the 6 versus 12 mL/kg IBW (ARDSNET, 2000). Today, best evidence demonstrates that using tidal volumes of 6 mL/kg IBW or less are associated with the greatest mortality benefit (Bein et al., 2016). Therefore, the variable tidal volumes in these studies, none of which reached or were below 6 mL/kg IBW, may contribute to the variability of results. Furthermore, the study design by Papazian et al. (2010)* was based on an estimated mortality rate of around 50%. It may be that their use of lower tidal volumes affected the mortality of both arms, resulting in underpowering of the study for the primary outcome of 90-day mortality.

Recruitment time frame. The design of all 3 studies involved recruiting patients within 36–48 hours of first meeting ARDS criteria (defined by PaO_2/FiO_2 ratio and PEEP). This may affect outcomes because data have shown that oxygenation in ARDS is most unfavorable in the first 48 hours (Michael et al., 1998). If patients were not recruited and receiving treatment during the first 48 hours, the effect of the treatment may be diminished. Furthermore, it takes time to initiate the study protocol, suggesting that even more time may have lapsed before the initiation of the intervention. Therefore, late recruitment and initiation of treatment may result in missing the time frame where the intervention has the most opportunity to have a beneficial effect.

Inclusion. Variability among ARDS inclusion criteria between the three studies may affect interpretation and generalizability of findings. The studies by Forel et al. (2006) and Papazian et al. (2010) set the ARDS inclusion criteria at PaO_2/FiO_2 ratio of ≤150, whereas the study by Gainnier et al. (2004) included patients with a PaO_2/FiO_2 ratio of ≤200, which by today's Berlin criteria includes both moderate and severe ARDS (Ferguson et al., 2012). The risks versus benefits of the use of NMBAs may not be equal across varying severities of ARDS.

Adverse effects of NMBA

Many clinicians are hesitant to initiate the use of NMBAs for several reasons. The general trend in management toward lower sedation and more awake patients runs contrary to the high doses of sedation necessary during paralysis with NMBAs. With NMBAs, a thorough neurological examination becomes impossible, introducing the risk of neurological injury, which may go undetected during the paralysis period. Most concerning for many clinicians is the perceived risk for muscle weakness, critical illness polyneuropathy and critical illness

myopathy (CIP/CIM). About 60% of patients with ARDS will develop CIP/CIM; however, 49–77% of patients in the ICU for at least 7 days will develop CIP/CIM, regardless of diagnosis (Hermans et al., 2007). There are confounding studies showing correlations, but no definitive link between NMBAs and CIP/CIM (Crespo & James, 2016). Additionally, several studies have shown no correlation between NMBAs and increased risk for CIP/CIM (Bednarík, Vondracek, Dusek, Moravcova, & Cundrle, 2005; de Jonghe et al., 2002; de Letter et al., 2001).

All the three primary studies discussed above reported incidence of CIP/CIM, although neither were primary outcome measures. Two systematic reviews and meta-analyses evaluated the incidence of CIP/CIM and found no increased incidence (Alhazzani et al., 2013 and Neto et al., 2012). Therefore, it is reasonable to conclude that the risk is theoretical and should not preclude the use of treatment that is evidence based.

Secondary analyses

Secondary analyses of all three primary studies were conducted by two separate groups. Neto et al., 2012 concluded from their data analysis that the number needed to treat (NNT) was eight for 28-day mortality when considering the studies by Papazian et al. (2010) and the Forel et al. (2006)* studies. When considering all three studies, the NNT for survival to intensive care discharge was eight, and for survival to hospital discharge was nine (Alhazzani et al., 2013). Both secondary analyses concluded the data were strong enough to support the use of NMBAs for the treatment of ARDS (Alhazzani et al., 2013; Neto et al., 2012). Furthermore, both groups analyzed data regarding CIP/CIM in the three primary studies. Although none of the primary studies conducted electromyography studies to assess CIP/CIM, they did report their observational data. Based on the analysis of that data, Alhazzani et al., 2013 and Neto et al., 2012 both conclude that there is no evidence of increased risk of CIP/CIM from the primary RCT, and therefore, concern for CIP/CIM should not preclude the use of NMBAs in ARDS.

Future research

Over the past 20 years, ARDS management has become more uniform, as the efficacy of certain strategies has become more clear. Standards of care for ARDS now specifically state that tidal volumes of 6 mL/kg IBW should be used with high PEEP ventilatory strategies (Bein et al., 2016). However, uncertainty persists whether early intervention with NMBAs promotes significantly better outcomes. Currently underway is the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial, which has been designed to look at the safety and efficacy of early use of NMBAs in ARDS (Huang et al., 2017). The ROSE trial was designed to build off the study by Papazian et al. (2010), and specifically controls for earlier recruitment, LTVV, high PEEP, and is powered for half the effect of the study by Papazian et al., so an unexpected decreased mortality will not result in underpowered conclusions (Huang et al., 2017).

Conclusion

Based on the current available data, it is appropriate to use NMBAs in ARDS. Although the three primary studies discussed have limitations, they all show improved outcomes in either primary or secondary measures (Forel et al., 2006; Gainnier et al., 2004; Papazian et al., 2010). Two separate meta-analyses concluded that the NNT was between 8 and 9 for various mortalities (Alhazzani et al., 2013; Neto et al., 2012). Additionally, a primary risk associated with NMBA use is CIP/CIM, and several independent studies have shown no direct correlation between the use of NMBAs and CIP/CIM (Bednarík et al., 2005; de Jonghe et al., 2002; de Letter et al., 2001). Therefore, at this time, the evidence supports treating moderate-to-severe ARDS with NMBAs in conjunction with established standards of care.

Competing interests: *The author reports no conflicts of interest.*

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