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Neuromuscular Blocking Agent Use in Acute Respiratory Distress Syndrome: Which Variable is Important?

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Abstract

Background: The study of neuromuscular blocking agents (NMBAs) in the management of acute respiratory distress syndrome (ARDS) has provided conflicting results in terms of their effect on mortality.

Objectives: The main purpose of this study was to evaluate mortality in ARDS patients who underwent NMBA.

Methods: A retrospective secondary analysis of 4200 patients with ARDS was collected from two academic medical centers, Tehran, Iran. This study was performed to assess the impact of NMBAs use in ARDS patients with different subgroups including mild and moderate-to-severe ARDS, age more and less than 65 years, having medical turnover vs. not-having, and high acute nursing care vs. moderate to low nursing care.

Results: Intensive care unit (ICU) mortality has occurred in 1169 (27.8%) participants. The mortality rate was 28.6% and 27.5% in patients with mild and moderate-to-severe ARDS, respectively. In the subjects without medical turnover, the moderate dose of NMBAs significantly reduces the mortality of patients ($P=0.044$). In patients who need high acute nursing care, increasing the NMBAs dose significantly reduces patients' mortality ($P=0.010$). In addition, increasing the NMBAs doses significantly reduces ICU length of stay (LOS).

Conclusion: This study provides evidence that the administration of different doses of NMBAs had no effect on patients' mortality with mild or moderate-to-severe ARDS. However, higher doses of NMBAs than low doses increased the risk of mortality in patients over 80 years and can reduce the risk of death in patients less than 55 years.

Keywords: Respiratory Distress Syndrome, Acute, Neuromuscular Blocking Agents, Mortality

1. Background

Acute respiratory distress syndrome (ARDS) is an acute inflammatory process that impairs the capacity of the lungs to oxygenate, resulting in respiratory failure.[1] In spite of advanced therapeutic techniques, ARDS is still associated with poor prognosis.[2] The estimated incidence of ARDS globally ranges from 10 to 86 cases per 100 000 patients and hospital mortality related to ARDS is high, with rates reported ranging from 35% to 46%, depending on the severity of initial hypoxemia.[3,4] ARDS evolved within one week of exposure to a risk factor for ARDS.[5] Pneumonia, aspiration, inhalation injury, near drowning, and pulmonary contusion are risk factors which cause ARDS through direct lung injury. For the majority of ARDS cases, pneumonia and aspiration events are responsible.[6,7] In addition, other risk factors for ARDS that cause indirect lung injury are sepsis, pancreatitis, cardiopulmonary bypass, burns, injuries, hemorrhagic shock, transfusions, and an overdose of medication.[8,9]

Treatment of ARDS is also a multimodal strategy, which used both non-pharmacological and pharmacological treatment methods, in ARDS patients.[10,11] Non-pharmacologic mechanical ventilation (MV) strategies include low tidal volumes ventilation, open lung ventilation, low inspiratory pressures, high positive end-expiratory pressure (PEEP) and recruitment maneuvers

in patients with moderate to severe ARDS and prone positioning in patients with severe ARDS.[12-15] On the other hand, neuromuscular blocking agents (NMBAs) have been prescribed as a pharmacological treatment method for patients with ARDS to minimize inflammation, oxygen intake, and cardiac output, help to facilitate ventilation synchronization and thus reducing ARDS-related mortality.[16-19]

A meta-analysis by Tao et al[20] indicated that a 48 hours NMBA infusion might reduce intensive care unit (ICU) mortality in patients with moderate-to-severe ARDS. Furthermore, a recent systematic and meta-analysis by Chang et al[21] showed that the use of NMBAs could significantly decrease mortality in moderate-to-severe ARDS patients and reduce the incidence of barotrauma during MV. However, Honor et al[22] pointed out that the conclusions of Chang et al,[21] are not the recommendations of the experts focusing upon the most hypoxemic patients and this message seems crucial to considering the numerous side effects of NMBAs. However, the benefit of NMBA was not confirmed by a recently published randomized controlled trial (RCT), the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial,[23] leaving the use of NMBA in ARDS patients unclear and controversial. Therefore, it seems that the therapeutic role of NMBA in patients with ARDS is still an open field to explore. Accordingly, we conducted this observational retrospective secondary analysis on the database of the 4200 patients with ARDS from the mixed medical–surgical ICUs of two academic medical centers in Iran, to assess mortality in ARDS patients who underwent NMBA.

2. Objectives

The main purpose of this study was to evaluate mortality in ARDS patients who underwent NMBA.

3. Methods

3.1. Study Design and Participants

This study was a retrospective secondary analysis of an original project that was prospective longitudinal cohort study.[24] In brief, the original study was a prospective longitudinal cohort study was conducted of 4200 mixed medical–surgical ICUs patients with ARDS on MV from of two academic teaching hospitals in Tehran, Iran between June 1, 2007 and October 31, 2015.[24] This secondary analysis study was performed to assess the impact of NMBAs use in ARDS patients with different subgroups including mild and moderate-to-severe ARDS, age more and less than 65 years, having medical turnover vs. not-having, and high acute nursing care vs. moderate to low nursing care. The patients, or their relatives, were informed about participation in the study by the physician at the time of admission with consent in all cases. All study parts were reviewed according to the "Strengthening the Reporting of Observational Studies in Epidemiology for respondent-driven sampling studies" (STROBE-RDS) statement.[25]

3.2. Eligible Criteria

The inclusion criteria were: (*a*) age ≥ 18 years, (*b*) intubated and mechanically ventilated patients with ARDS, (*c*) PaO_2/FiO_2 less than 150 with PEEP at least 5 within the first 48 hours of the onset of ARDS (*d*) full-code status, and (*e*) informed consent obtained from the patient, legal guardian, or healthcare surrogate. Exclusion criteria included pregnancy, patient receiving continuous infusion of NMBA, known NMBA allergy, contraindication to introduction of nasogastric tube, undrained pneumothorax, treatment with extracorporeal membrane oxygenation or extracorporeal CO_2 removal, increased intracranial pressure, respiratory chronic insufficiency, body mass index greater than 40 kg/m^2, severe chronic liver disease (Child–Pugh class C), bone marrow transplantation or chemotherapy-induced neutropenia, burn lesions greater than 30% of body surface, Simplified Acute Physiology Score (SAPS) II of 70 or greater.

Moderate-to-severe ARDS patients diagnosed according to the Berlin criteria,[26] or American-European Consensus Conference (AECC) criteria[27]; which were characterized by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) of less than 150 mm Hg with a PEEP at least 5 cm of water within the first 48 hours of the onset of ARDS. In addition, NMBAs doses (determined in accordance with published recommendations in three levels high, moderate, and low.[28] The NMBAs dose is cumulative one.

3.3. Data Collection and Outcome

Demographic and clinical characteristics were recorded for all participants, including age, gender, acute nursing care determined by requiring > 8 hours nursing care in an 8-hour shift, staff burnout and anticipated turnover measured with the Anticipated Turnover Scale questionnaire,[29] ICU length of stay (LOS), free-ICU days, sedative dose which determined in accordance with published recommendations.[30] Additionally, illness severity was measured by the Simplified Acute Physiology Score (SAPS) II at the day of ICU admission.[31] The main outcome variable was ICU mortality, following ICU admission.

3.4. Statistical Analysis

Data are presented as mean ± standard deviation (SD) or percentages. Categorical data were compared using the χ^2 test (or Fisher exact test when appropriate); and continuous data, using the Student *t* test. In addition, both unadjusted and adjusted logistic regressions were used to estimate the odds ratio (OR) to determine the association of demographic and clinical characteristics with mortality. All data were analyzed using the Statistical Package for the Social Sciences (SPSS) 21.0 (Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA),[32] and two-side $P < 0.05$ indicated a statistically significant difference.

4. Results

4.1. Demographic and Clinical Characteristics

A total of 4200 subjects were included in the second analysis. The mean ± SD age of total participants was 67.25 ± 11.5 years and near to half of the patients were over 65 years (n = 2051, 48.8%) and 58.1% of the included patients were female. According to the Berlin criteria,[26] more than half of the participants were recognized with moderate-to-severe ARDS (n = 3031, 72.16%) and the other patients (n = 1169, 27.84%), with mild ARDS. The mean ± SD age of patients with moderate-to-severe ARDS was 67.29 ± 11.59 years, more than half of the patients were over 65 years (51%), and 1770 (58.4%) patients were female, which was not significantly different from patients with mild ARDS ($P > 0.05$). In addition, in the patients with mild and moderate-to-severe ARDS did not differ significantly in terms of having medical turnover vs. not-having, and high acute nursing care vs. moderate to low nursing care ($P > 0.05$).

4.2. NMBA Doses in Two Groups of Study

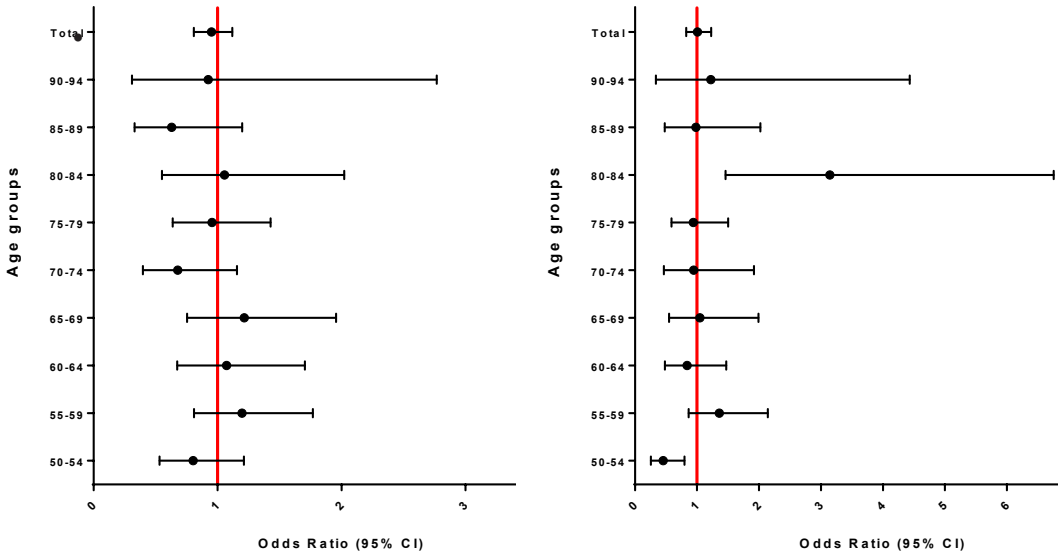
A total of 2254 (53.75) subject received moderate dose of NMBA, and the other patients received low 1055 (25.1%) and high 891 (21.2%) dose of NMBA, respectively. In mild ARDS patients group low, moderate and high doses of NMBA were used in 287 (24.5%), 609 (52.5%), and 273 (23.3%) patients, respectively. In patients with moderate-to-severe ARDS, 768 (25.3%), 1645 (54.3%), and 618 (20.4%) patients received low, moderate and high doses of NMBA, respectively. The results show that not only was there no statistically significant difference between the two groups ($P > 0.05$), but also there was no statistically significant difference even within group ($P > 0.05$).

4.3. Outcome

ICU mortality has occurred in 1169 (27.8%) participants. The mortality rate was 28.6% and 27.5% in patients with mild and moderate-to-severe ARDS, respectively. Mortality was not significant between the two groups of study. Effect of different doses of NMBAs on mortality according to demographic and clinical characteristics of participants are presented in Table 1. According to Table 1, the increasing NMBAs doses had no effect on patients' mortality with mild and moderate to severe ARDS. High doses of NMBA significantly increased mortality in patients over 65 years ($P = 0.036$). In the subjects without medical turnover, the moderate dose of NMBAs significantly reduces the mortality of patients ($P = 0.044$). In patients who need high acute nursing care, increasing the NMBAs dose significantly reduces patients' mortality ($P = 0.010$). In addition, increasing the NMBAs doses significantly reduces ICU LOS ($P < 0.001$). However, it had no effect on the free-ICU days ($P = 0.168$). Logistic regression (Figure 1) revealed that the high dose vs. low dose of NMBAs was increased the risk of mortality among patients between 80 to 84 years old (odds ratio [OR]: 3.142, 95% CI: 1.461-6.756, $P = 0.003$). However, higher doses of NMBA than low doses reduce the risk of death in patients between 50 and 54 years of age (OR: 0.432, 95% CI: 0.267-0.798, $P = 0.006$). Accordingly, the effect of moderate and low dose of NMBAs was similar on mortality according to the age groups.

5. Discussion

In this secondary analysis study, we evaluated the administration of different doses of NMBA (low to high doses) in patients with mild and moderate-to-severe ARDS and its effect on patient mortality. The results indicated that the increasing NMBAs doses had no effect on patients' mortality with mild and moderate-to-severe ARDS. However, increasing the NMBAs doses significantly reduces ICU LOS. In addition, the high dose vs. low dose of



Moderate NMBAs dose vs. Low dose | High NMBAs dose vs. Low dose

Figure 1. Logistic Regression Analysis of the Effect of NMBAs Doses on Mortality According to age Groups.

Table 1. Effect of different doses of NMBAs on mortality according to demographic and clinical characteristics of participants

Variables	Outcomes		Total	*P*-value
	Death	Alive		
Patients with Mild ARDS				
High dose of NMBAs	82 (30.0)	191(70.0)	273 (100)	0.513
Moderate dose of NMBAs	165 (27.1)	444 (72.9)	609 (100)	
Low dose of NMBAs	87 (30.3)	200 (69.7)	287 (100)	
Total	334 (28.6)	835 (71.4)	1169 (100)	
Patients with moderate to severe ARDS [a]				
High dose of NMBAs	172 (27.8)	446 (72.2)	618 (100)	0.981
Moderate dose of NMBAs	451 (27.4)	119 (72.6)	1645 (100)	
Low dose of NMBAs	212 (27.6)	556 (72.4)	768 (100)	
Total	835 (27.5)	2196 (72.5)	3031 (100)	
Age <65 years				
High dose of NMBAs	117 (25.0)	351 (75.0)	648 (100)	0.258
Moderate dose of NMBAs	340 (28.7)	843 (71.3)	1183 (100)	
Low dose of NMBAs	145 (29.1)	353 (70.9)	498 (100)	
Total	602 (28.0)	1547 (72.0)	2149 (100)	
Age >65 years				
High dose of NMBAs	137 (32.4)	286 (67.6)	423 (100)	0.036*
Moderate dose of NMBAs	276 (25.8)	795 (74.2)	1071 (100)	
Low dose of NMBAs	154 (27.6)	403 (72.4)	557 (100)	
Total	567 (27.6)	1484 (72.4)	2051 (100)	
Patients with medical turnover [b]				
High dose of NMBAs	150 (27.7)	391 (72.3)	541 (100)	0.631
Moderate dose of NMBAs	407 (29.3)	984 (70.7)	1391 (100)	
Low dose of NMBAs	162 (27.4)	430 (72.6)	592 (100)	
Total	719 (28.5)	1805 (71.5)	2524 (100)	
Patients without medical turnover [b]				
High dose of NMBAs	104 (29.7)	246 (70.3)	350 (100)	0.044*
Moderate dose of NMBAs	209 (24.2)	654 (75.8)	863 (100)	
Low dose of NMBAs	137 (29.6)	326 (70.4)	463 (100)	
Total	450 (26.8)	1226 (73.2)	1676 (100)	
Patients who need moderate to low nursing care [c]				
High dose of NMBAs	214 (29.3)	516 (70.7)	730 (100)	0.288
Moderate dose of NMBAs	487 (27.2)	1306 (72.8)	1793(100)	
Low dose of NMBAs	212 (25.8)	611 (74.2)	823 (100)	
Total	913 (27.3)	2433 (72.4)	3346 (100)	
Patients who need high nursing care [c]				
High dose of NMBAs	40 (24.8)	121 (75.2)	191 (100)	0.010*
Moderate dose of NMBAs	129 (28.0)	332 (72)	461(100)	
Low dose of NMBAs	87 (37.5)	145 (65.5)	232 (100)	
Total	256 (30.0)	598 (70.0)	854 (100)	

[a] As determined by a ratio of PaO2/FiO2 <150 mm Hg with a PEEP at least 5 cm of water within the first 48 h of the onset of ARDS
[b] As determined by the anticipated turnover scale (ATS)
[c] As determined by requiring >8 hours nursing care in an 8 hour shift

NMBAs was increased the risk of mortality among patients between 80 to 84 years old. However, higher dose of NMBA than low doses reduce the risk of death in patients between 50 and 54 years of age.

Gainnier et al[33] conducted a multi-center, prospective controlled randomized trial and found that the use of NMBAs during a 48-hour period in ARDS patients was associated with a sustained improvement in oxygenation. In the ACURASYS trial, Papazian et al[19] found that in patients with severe ARDS, early administration of

cisatracurium continuously for 48 hours improved the adjusted 90-day survival, decreased the risk of barotrauma, and increased the time off the ventilator without increasing muscle weakness. However, more recent results from the ROSE trial failed to show reductions in mortality when NMBAs were administered in moderate-severe ARDS.[23] While cisatracurium has been shown to have anti-inflammatory properties in animal models,[34] its clinically applicable advantage is likely to include the avoidance of ventilator dyssynchrony and lung compliance improvements.[35] The results of three recent meta-analyses have all demonstrated that NMBA administration in ARDS patients is associated with reduced barotrauma and improved oxygenation; however, the impact on mortality remains controversial.[21,36,37]

On the other hand, data regarding the compare of different doses of NMBAs in critically ill patients with ARDS is limited. Two studies have used cisatracurium 15 (mg) as a continuous infusion NMBA at a set rate of 37.5 mg/h × 48 h to demonstrate a mortality benefit with NMBA for ARDS patients.[19,38] A study by Papazian et al[19] showed the positive effects of cisatracurium on 28- and 90-day mortality rates compared to patients did not receive NMBA. However, they reported significant adverse effects in the control group compared with the NMBA group. The high set rate of NMBA is a criticism of this research, possibly contributing to overexposure and adverse effects.

In the present study, high doses of NMBA increased the risk of mortality in patients between the ages of 80 and 84 years, while higher doses of NMBA reduced the risk of death in patients between 50 and 54 years of age. This could be related to the risk associated with high doses of NMBA in very old intensive care patients (≥80 years). The use of NMBAs in critically ill patients can be further complicated by drug interactions, alterations in pH and electrolytes, venous thromboembolisms, myopathy and prolonged recovery. In addition, in patients with ARDS, the rate of acquired ICU weakness is reported to be between 30 and 60%, which can increase with older age, female gender, multi-organ failure, administration of corticosteroids, and prolonged durations of vasopressor support, MV, and ICU length of stay.[39,40] Therefore, high doses of NMBA in older ICU patients with ARDS can increase patients' risk and ultimately increase mortality in these individuals.

The strengths of our study included the large sample size and its multi-center design. However, our study has a several limitations. First, data were collected prospectively in the original study, but data analysis on NMBA was performed retrospectively. Second, due to the retrospective nature of the study, we were not able to evaluate adverse effects associated NMBA in ICU patients. However, our results provide insights into abusers of high dose of NMBA in older age patients that need further reflection and study.

6. Conclusion

This multicenter retrospective observational study provides evidence that the administration of different doses of NMBAs had no effect on patients' mortality with mild or moderate-to-severe ARDS. However, higher doses of NMBAs than low doses increased the risk of mortality in patients over 80 years and can reduce the risk of death in patients less than 55years. So, patients should be carefully monitored while receiving NMBAs and only short durations of use should be prescribed to prevent further complications, especially in older patients. Future studies are needed to replicate and expand these findings before they can be widely adopted in clinical practice.

Research Highlights

What Is Already Known?

- Treatment of ARDS is also a multimodal strategy, which used both non-pharmacological and pharmacological treatment methods, in ARDS patients.
- NMBAs have been prescribed as a pharmacological treatment method for patients with ARDS to minimize inflammation, oxygen intake, and cardiac output, help to facilitate ventilation synchronization and thus reducing ARDS-related mortality.

What DoesThis Study Add?

- The increasing NMBAs doses had no effect on patients' mortality with mild and moderate-to-severe ARDS.
- Increasing the NMBAs doses significantly reduces ICU LOS.
- The high dose vs. low dose of NMBAs was increased the risk of mortality among patients between 80 to 84 years old. However, higher dose of NMBA than low doses reduce the risk of death in patients between 50 and 54 years of age.
- Patients should be carefully monitored while receiving NMBAs and only short durations of use should be prescribed to prevent further complications, especially in older patients.

Authors' Contributions

FR, MS, MKH, and AV-A designed the study and were responsible for the data acquisition, data analysis, and interpretation, and both authors substantively revised and approved the submitted version of the manuscript

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Ethical Approval

Current study was approved by the Investigative Review Board at Baqiyatallah University of Medical Sciences, Tehran, Iran (IR.BMSU.REC.1394.451) and Shariati Hospital of Tehran University of Medical Sciences, Tehran, Iran.

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