The Use of Paralytics in Patients with Acute Respiratory Distress Syndrome

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KEYWORDS

• Acute respiratory distress syndrome • Mechanical ventilation • Neuromuscular blocking agents • Protective ventilation • Spontaneous ventilation • Transpulmonary pressure • ICU-acquired weakness

KEY POINTS

- Neuromuscular blocking agents (NMBAs), largely used in the treatment of acute respiratory distress syndrome (ARDS), have been shown to improve the oxygenation and decrease the mortality of the most hypoxemic patients.
- NMBAs most likely decrease ventilator-induced lung injury by facilitating the adaptation to protective ventilation and prevention of high levels of transpulmonary pressures, and by limiting barotrauma and biotrauma. NMBAs also limit the derecruitment induced by active expiration.
- The use of NMBAs should be considered in the most severe ARDS patients at the early phase of the injury and for a limited period. In the less hypoxemic forms and/or after the improvement of oxygenation, spontaneous ventilator efforts should be maintained.

INTRODUCTION

Almost 50 years after its first description,[1] acute respiratory distress syndrome (ARDS) remains a hot topic, and its definition and treatment are still debated. The mortality of ARDS patients remains high (40%–50% of patients) despite medical advances.[2] The recent definition of the European Society of Intensive Care Medicine (ESICM) task force[3] has identified 3 levels of severity that are associated with significantly different prognoses and management strategies. For the last 15 years, only 3 therapeutic strategies have been shown to increase the survival of ARDS patients in randomized controlled trials (RCTs). A reduction in the tidal volume[4] has now entered the current standard of care.[5] Two other recent studies have unsettled the management of more severe ARDS patients[6,7]: the administration of neuromuscular blocking agents (NMBAs) for a 2-day period in the early phase of ARDS and the use of prone positioning (PP). These 2 recent advances are frequently associated, and call into question the ventilatory strategy in early ARDS. Consequently, exploration of the role of NMBAs in the care of such patients must define the respective role of entirely controlled ventilation versus ventilation allowing a part of spontaneous breathing (SB). The purpose of this review is to recall both older and more recent literature with a focus on NMBAs in ARDS, thereby to propose a pathophysiologic explanation for the actions of NMBAs and to

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attempt to define their place in the ventilation strategy for the treatment of patients with ARDS.

FROM CASE REPORTS TO RANDOMIZED CONTROLLED TRIALS: THE SAGA OF NEUROMUSCULAR BLOCKING AGENTS IN ACUTE RESPIRATORY DISTRESS SYNDROME

Clinical Practice

NMBAs are frequently used by intensivists, especially for the management of ARDS; in a recent large survey[8,9] 25% to 55% of ARDS patients were involved. Indeed, the adaptation of the patients to the ventilator, the control of patient/ventilator asynchrony, the use of low tidal volumes, the use of permissive hypercapnia, and the use of PP or high-frequency oscillatory (HFO) ventilation is cited to justify this large use.[9,10] Moreover, several RCTs studying the effects of tidal volume, positive end-expiratory pressure (PEEP), or HFO report the frequent use of NMBAs.[4,11–13]

Historical Context

Despite their frequent use, the guidelines concerning the use of NMBAs have not been revised since 2002[14] and have included paralytics for facilitating mechanical ventilation (MV) when sedation alone is inadequate, most notably in patients with severe gas-exchange impairment. Regarding the recent data in the literature, these guidelines appear to be restrictive and outdated. The first publications concerning NMBAs were case reports and small nonrandomized studies that reported controversial results concerning the improvement in oxygenation.[15–18] Physiologic studies on ventilator mechanics in healthy subjects found that sedation induced a reduction in pulmonary compliance, whereas NMBAs induced an increase in thoracic compliance[19] and improved the mechanical viscoelastic properties of the chest wall.[20] The absence of strong data showing a benefit to the prognosis or potential adverse events, especially intensive care unit (ICU)-acquired neuromyopathy,[21] were often responsible for a distrust of paralytics. Larger studies focusing on the clinical effects of paralytics in ARDS patients began with Lagneau and colleagues,[22] who demonstrated that the continuous infusion of NMBAs for 2 hours improved the partial pressure of arterial oxygen (Pa_{O_2})/fraction of inspired oxygen (Fi_{O_2}) ratio in a prospective randomized control trial (PRCT) including 102 patients presenting moderate to severe ARDS (**Table 1**).

The Era of Randomized Controlled Trials

Recent randomized studies have helped to clarify positions. In the first multicenter PRCT conducted by Gainnier and colleagues,[23] there was a significant improvement in the Pa_{O_2}/Fi_{O_2} ratio in the group of patients with ARDS receiving neuromuscular blockade continuously for 48 hours. The beneficial effects were observed as early as the 48th hour and persisted throughout the study

Table 1
Main characteristics and results of clinical studies investigating the effect of NMBAs on oxygenation in ARDS patients

Authors,[Ref.] Year	No. of Patients	Study Design	Setting	Type of Lung Failure	Drug Infused	Duration of Infusion	Effect on Oxygenation
Bishop,[16] 1984	9	NRCT	ICU	4 ALI/5 ARDS	Pancuronium	Single bolus	No effect
Coggeshall et al,[17] 1985	1	Case	ICU	1 ARDS	Pancuronium	Repeated boluses	Improvement
Conti et al,[18] 1985	13	PNRCT	ICU	9 ALI/4 ARDS	Pancuronium	Single bolus	No effect
Lagneau et al,[22] 2002	102	PRCT	ICU	102 ARF with Pa_{O_2}/Fi_{O_2} <200	Cisatracurium	2 h	Improvement
Gainnier et al,[23] 2004	56	PRCT	ICU	56 ARDS (Pa_{O_2}/Fi_{O_2} <150)	Cisatracurium	48 h	Improvement
Forel et al,[24] 2006	36	PRCT	ICU	36 ARDS (Pa_{O_2}/Fi_{O_2} <200)	Cisatracurium	48 h	Improvement
Papazian et al,[6] 2010	339	PRCT	ICU	339 ARDS (Pa_{O_2}/Fi_{O_2} <150)	Cisatracurium	48 h	Improvement

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; Fi_{O_2}, fraction of inspired oxygen; ICU, intensive care unit; NRCT, nonrandomized controlled trial; Pa_{O_2}, partial pressure of arterial oxygen; PNRCT, prospective nonrandomized controlled trial; PRCT, prospective randomized controlled trial.