Neuromuscular-Blocking Agent Use in Critically Ill Patients

Abstract
Neuromuscular-blocking agents (NMBAs) are a cornerstone in the management of critically ill patients. There is evidence supporting short course (<48 h) of paralysis for patients with moderate-to-severe acute respiratory distress syndrome with PaO2/FiO2 ratio <150. Proper knowledge of these agents and their evidence-based use is fundamental. Health-care providers can play an important role in the regulation and the use of NMBAs in critically ill patients.

Introduction
Neuromuscular-blocking agents (NMBAs) play an important role in the management of critically ill patients. Their use is common in situations where patient paralysis is required like in surgical anesthesia and rapid sequence intubation (RSI).

Other indications include the management of acute respiratory distress syndrome (ARDS), increased intracranial and abdominal pressure, and prevention of shivering during therapeutic hypothermia. NMBAs are classified based on their chemical structures, mechanism of action (depolarizing and nondepolarizing), and pharmacokinetic properties including their duration of action (short, intermediate, and long acting). Depolarizing agents bind and activate nicotinic acetylcholine receptors causing persistent depolarization, which then render muscle fibers resistant to further cholinergic stimulation.

Succinylcholine is the only available depolarizing NMA that is commonly used as the drug of choice for urgent intubation because of its quick onset and short duration. Nondepolarizing NMBAs are highly ionized water-soluble compounds, which bind to acetylcholine receptor and act as competitive antagonists. They can be divided into either aminosteroidal or benzylisoquinolinium nucleus and vary in their onset and duration of action. NMBAs have a different variety of pharmacokinetic profiles that can be utilized depending on the situation. For instance, rapid onset and short duration are of value in RSI.

In contrast, those with a longer duration are useful in surgeries. Table 1 depicts an overview of commonly used NMBAs.

Clinical Usage
Rapid sequence intubation
RSI is used to secure a definitive airway in critically ill patients who are unstable and uncooperative or may be at risk of aspiration. Their use has been associated with a lower prevalence of hypoxemia, procedure-related complications, and improved intubating conditions with fewer attempts.

Succinylcholine and rocuronium are commonly used for intubation given the advantage of their short onset and duration of action. A large Cochrane review found succinylcholine (minimum dose, 1 mg/kg) to be superior to rocuronium (minimum dose, 0.6 mg/kg) with regard to favorable intubation conditions. There was no difference in intubation conditions when succinylcholine was compared with higher doses of rocuronium (0.9–1.2 mg/kg), but the shorter duration of action with succinylcholine made it more favorable clinically.

However, several important contraindications to its use in critically ill patients with a history of malignant hyperthermia or hyperkalemia made clinicians to prefer rocuronium as a viable option for RSI. Allergy to aminosteroids is the only absolute contraindication for rocuronium.

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Access this article online
Website: www.sccj-sa.org

How to cite this article: Al Harbi SA, Almodaimegh HS, Arabi YM. Neuromuscular-blocking agent use in critically ill patients. Saudi Crit Care J 2019;3:XX-XX.
Acute respiratory distress syndrome

Mechanical ventilation remains the basis of supportive treatment for ARDS. It involves the use of sedation to allow for patient comfort while on the ventilator. In some circumstances, sedation is not sufficient and other adjunct medications are needed. The current evidence investigated the outcomes of using NMAs in ARDS for a short period of time. A review article by Boureme et al. illustrated that approximately 25%–45% of ARDS patients require NMAs for an average of 1 ± 2 days and the main indications for initiating are hypoxemia and need for mechanical ventilation. In 2016, Murray et al. recommended a short course (<48 h) of paralysis for patients with moderate-to-severe ARDS (PaO2/FiO2 ratio <150). In 2017, the Surviving Sepsis Campaign also recommended a trial of NMB therapy for severe ARDS. A randomized controlled trial (RCT) by Gainnier et al. demonstrated the benefit of NMAs, mainly with cisatracurium, on oxygenation for patients with moderate-to-severe ARDS. The outcome of the above-mentioned trials indicates that the use of NMAs, mainly cisatracurium, in severe ARDS as a continuous infusion for 48 h or less, may be beneficial. Furthermore, it is important to realize that their use in ARDS is still considered a last resort and that they are used when adequate sedation and appropriate ventilator adjustments have been done.

Elevated intra-abdominal pressure

NMAs may be used for preventing abdominal compartment syndrome, which is defined as an elevated intra-abdominal hypertension of 20 mmHg, and ultimately decompressive laparotomy for those patients with elevated intra-abdominal pressures (IAPs) through the reduction of abdominal wall muscle tone.

Elevated intracranial pressure

Routine use of NMAs in the management of elevated intracranial pressures is not recommended. NMAs should only be considered in the management of elevated intracranial pressures when deep sedation is insufficient for controlling the persistent increase in intracranial pressure. NMAs can either prevent or decrease the sympathetic and reflex response to tracheal suctioning, which would otherwise elevate intracranial pressure. NMAs help to facilitate mechanical ventilation (carbon dioxide

**Table 1: Overview of various neuromuscular-blocking agents**

<table>
<thead>
<tr>
<th>NMBA</th>
<th>Depolarizing agent</th>
<th>Aminosteroidal agents</th>
<th>Benzyloquinolinium agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Succinylcholine</td>
<td>Pancuronium</td>
<td>Vecuronium</td>
</tr>
<tr>
<td>Initial dose (mg/kg)</td>
<td>1.5</td>
<td>0.06-0.1</td>
<td>0.6-1.2</td>
</tr>
<tr>
<td>Onset (time to peak effect)</td>
<td>30-60 s</td>
<td>3-5 min</td>
<td>1-2 min</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>10</td>
<td>90-100</td>
<td>25-50</td>
</tr>
<tr>
<td>Infusion dose (mcg/kg/min)</td>
<td>Not recommended</td>
<td>1-2</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Recovery (min)</td>
<td>5-10 min</td>
<td>120-180</td>
<td>55-160</td>
</tr>
<tr>
<td>Percentage renal excretion</td>
<td>Metabolism via plasma cholinesterase</td>
<td>Increased effect</td>
<td>Increased duration</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Increased effect</td>
<td>Increased effect</td>
<td>Increased effect</td>
</tr>
<tr>
<td>Percentage biliary excretion</td>
<td>10-15</td>
<td>50-70</td>
<td>35-50</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>Mild increased effect</td>
<td>Moderate</td>
<td>Variable, mild increased effect</td>
</tr>
<tr>
<td>Active metabolites</td>
<td>None</td>
<td>3-desacetylpancuronium (50% potency)</td>
<td>None</td>
</tr>
<tr>
<td>Histamine release</td>
<td>+</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Effects on cardiac</td>
<td>Vagal block (tachycardia)</td>
<td>N/A</td>
<td>Modest to marked</td>
</tr>
<tr>
<td></td>
<td>Prolonged ICU block</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Evidence for critical illness polyneuromyopathy</td>
<td>N/A</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

+: Minimal, ++: Moderate, +++: Marked. NMBA: Neuromuscular-blocking agent, CNS: Central nervous system, N/A: Not applicable
elimination and lower positive end-expiratory pressure), decrease metabolic expenditure, and limit elevations in intracranial pressure after stimulating procedures.\[^7\] They can also decrease respiratory drive and IAP, thus improving cerebral flow both toward and away from the brain. The use of NMBAs in traumatic brain injury has not been demonstrated to improve long-term patient outcomes. In addition, it leads to difficulties in monitoring neurological function and seizure activity.\[^{17,18}\]

**Therapeutic hypothermia after cardiac arrest**

NMBAs have been used to prevent or treat shivering associated with therapeutic hypothermia. Shivering leads to heat production, inflammation, elevated intracranial pressure, decreased brain tissue oxygen levels, and increased metabolic rate. Retrospective studies showed conflicting data on survival rates and complications that lead the American Heart Association guidelines to recommend the avoidance or minimal use of NMBAs.\[^{15}\]

**Monitoring**

NMBAs should be used to recommend the avoidance or minimal use of NMBAs. It is critical that patients are sedated and pain free before initiating NMBAs. Furthermore, NMBAs should be titrated to the lowest effective dose. A prospective, randomized, controlled investigation was conducted in 77 critically ill medical patients to compare outcomes between two different monitoring methods of neuromuscular blockade.\[^{19}\] Vecuronium doses were individualized by peripheral nerve stimulation (TOF) in the treatment group and by standard clinical assessment in the control group. Although TOF monitoring was performed in the control group, the nursing and house staff were blinded to the results and dosage adjustments were made according to a protocol. The mean TOF value at drug discontinuation was significantly lower in the standard clinical assessment group compared to the TOF group. There was less drug used to achieve 90% blockade (TOF = 1) in the patients monitored by TOF compared to those monitored by standard clinical assessment. The mean infusion rate and cumulative amount of drug used were also significantly lower in the TOF group. Recovery to a TOF of 4 out of 4 twitches and return of spontaneous ventilation were significantly faster in the TOF group. The incidence of prolonged paralysis was significantly higher in the standard clinical assessment group. Overall, 71% of patients (including patients from both groups) had abnormal neurologic examinations following discontinuation of vecuronium.\[^{19}\]

In another trial, medical intensive care unit (ICU) patients receiving continuous infusions of cisatracurium were randomized to TOF monitoring (n = 16) or clinical assessment (n = 14).\[^{20}\] Clinical assessment consisted of adjusting the NMBAs based on observed responses of the patient. Specifically, nurses monitored patient-ventilator dyssynchrony defined as signs of “bucking” and elevated mechanical ventilation peak pressures. Total absence of patient-initiated breaths was a goal of clinical assessment only for those patients undergoing inverse-ratio ventilation. Demographics were similar between groups, and there were no differences in the total number of medications or medication type (corticosteroid, aminoglycoside, or clindamycin).\[^{20}\] In respect to the outcome measures of postparalytic recovery times, total time paralyzed before discontinuation of paralytic, total cisatracurium dose, or episodes of prolonged paralysis, there was no difference between groups. In addition, no cases of prolonged paralysis syndrome or clinical evidence of acute myopathy were noted.\[^{17,21}\]

**Complications**

The use of NMBAs in certain conditions has its benefits; however, there are complications associated with their use that should be considered. Among those are ICU-acquired prolonged weakness.\[^{22}\] Several studies have investigated associations between the use of NMBAs and prolonged weakness that include myopathy, polyneuropathy, and neuropathy. However, data were inconsistent and not controlled, and the relationship is still controversial. Further studies are needed to clarify the relationship of specific risk factors. A retrospective observational study in severe asthmatics demonstrated an increased incidence (30% vs. 10%) of skeletal myopathy with NMBAs administration (mean duration, 3.1 ± 2.3 days), with myopathy only associated with duration of muscle relaxation.\[^{22,23}\] Another retrospective study in patients with severe asthma also demonstrated a higher incidence of postextubation skeletal muscle dysfunction, and multiple logistic regression analysis demonstrated that NMBAs were independent predictors of overall morbidity.\[^{24}\] A prospective study of patients with sepsis demonstrated that NMBAs were an independent risk factor for the development of critical illness polyneuropathy, defined by electrophysiologic testing.\[^{21,25}\] In contrast, a prospective study by Fan et al. found that in patients with acute lung injury, the duration of bed rest during critical illness, but not systemic corticosteroid nor use of NMBAs, was independently associated with prolonged muscle weakness.\[^{26}\] Furthermore, a RCT by Papazian et al. showed no change in muscle strength testing at day or at ICU discharge in patients receiving 48-h cisatracurium infusions compared with placebo.\[^{27}\] Modern critical care practice moving toward minimizing and interrupting sedation may offer further reductions for the incidence of prolonged muscle weakness in the ICU by decreasing overall immobility.\[^{27,28}\]

Other complications of using NMBAs include the association with risk of thrombosis. One study found NMBAs to be the strongest predictor of deep vein thrombosis (DVT) incidence and encouraged procedures...
that reduce venous stasis (passive mobilization and elastic compression stockings) to increase the efficacy of pharmacologic DVT prophylaxis in patients who are paralyzed.\textsuperscript{[29]}

Paralysis may result in impaired eyelid closure and loss of corneal reflex, which place the cornea at risk for drying, scarring, ulceration, and infection and may lead to permanent visual loss. An RCT found that applying artificial tears, on a regular set schedule, was more effective than passive eyelid closure alone at reducing the incidence of corneal abrasions.\textsuperscript{[30]}

Skin breakdown, slowed gastrointestinal motility, peripheral muscle weakness, diaphragmatic atrophy, and myositis are other complications of immobility that may be managed with supportive care, changes in position and height of bed, and mobilization.\textsuperscript{[1,5,23,33]} Allergic reaction can occur after Sugammadex acts by forming unknown mechanism.

and theophylline can decrease NMBA activities by postsynaptic response to acetylcholine. Finally, ranitidine acts as a competitor of acetylcholine receptor. In addition, phenytoin depresses blockage. Carbamazepine acts as a competitor of medications that decrease NMBAs activity are calcium channel blockers, procainamide, quinidine, and furosemide prolog NMBA activity by decreasing the prejunctional acetylcholine release. Finally, steroids decrease end-plate sensitivity to acetylcholine and cyclosporine inhibits the metabolism of certain NMBAs.

**Conclusion**

NMBAs are a cornerstone in the management of critically ill patients. Therefore, proper knowledge of these agents and their evidence-based use is fundamental. Health-care providers can play an important role in the regulation and the use of NMBAs in critically ill patients.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**