

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

## NEUROMUSCULAR BLOCKING AGENTS (NMBAs) IN ADULT INTENSIVE CARE UNITS

### SUMMARY

There is a lack of data supporting improved long-term outcomes for NMBA use in patients other than for refractory hypoxemia / hypercarbia, muscle contractions associated with tetanus, refractory intra-abdominal or intracranial hypertension, and prevention of shivering during therapeutic hypothermia. These agents are associated with significant side-effects and should be reserved for these select clinical situations. Several adjunctive therapies are necessary in the paralyzed patient and must not be overlooked.

### RECOMMENDATIONS

- ① **Patients MUST be mechanically ventilated prior to administration of NMBAs.**
- ① **Adequate sedative and analgesic therapy MUST be provided prior to and for the duration of neuromuscular blockade.**
- ① **Prophylactic eye care should be administered to all patients for the duration of neuromuscular blockade.**
  
- **Level 1**
  - **None**
  
- **Level 2**
  - **NMBA therapy should be monitored using either clinical assessment of respiratory function or presence of shivering or peripheral nerve stimulation [Train of Four (TOF) monitoring].**
  - **A short course (< 48 hours) of NMBA therapy can be used to induce paralysis in patients with moderate to severe ARDS (PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 150).**
  - **Non-depolarizing NMBAs are the agents of choice for continuous infusions.**
    - **Cisatracurium is the NMBA of choice for renal and hepatic impaired patients.**
  
- **Level 3**
  - **There is inadequate data to support the routine use of NMBAs.**
  - **NMBAs should be reserved for the following situations:**
    - **Medical management of refractory intra-abdominal hypertension or elevated intracranial pressures**
    - **Facilitation of mechanical ventilation with refractory hypoxemia / hypercarbia**
    - **Treatment of muscle contractures associated with tetanus**
    - **Treatment of shivering during therapeutic hypothermia**
  - **Physical therapy should be provided to patients on NMBAs.**

### EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

### LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

## INTRODUCTION

Neuromuscular blocking agents (NMBAs) should be considered an intervention of last resort due to the risk of side effects associated with their use. According to a review by Prielipp in 1998, less than 5% of patients in the ICU receive continuous administration of NMBAs for more than 24 hours (1).

NMBAs induce reversible muscle paralysis. These agents are classified based upon their structure, mechanism of action, and pharmacokinetic properties. Mechanistically, they are classified as either depolarizing or non-depolarizing. Depolarizing agents bind to and activate nicotinic acetylcholine receptors resulting in depolarization of the postsynaptic membrane of striated muscle. Succinylcholine is the only depolarizing agent. Outside of rapid sequence intubation (RSI), it has limited application in the ICU setting due to its short half-life and rapid onset of action. Succinylcholine is metabolized much more slowly than acetylcholine, thus prolonged stimulation of muscle can lead to extracellular shift of potassium and dysrhythmias or death. Non-depolarizing agents are highly-ionized, water-soluble compounds which also bind to acetylcholine receptors, but instead of activating them act as competitive antagonists. Non-depolarizing NMBAs have either an aminosteroidal or benzyliisoquinolinium nucleus. Non-depolarizing agents vary in onset and duration of action.

Pharmacokinetically, NMBAs differ in their duration of action and route of elimination. Additionally, differences exist in the degree of histamine release, vagal block, risk of prolonged blockade, and cost. See Table 2 for a complete overview of commonly used NMBAs.

NMBA infusions are discontinued to allow muscular function to gradually recover as the agent is metabolized and eliminated. If rapid reversal is required, anticholinesterase agents (edrophonium, neostigmine, pyridostigmine) along with antimuscarinic agents (glycopyrrolate, atropine) can be used. The newest reversal agent, sugammadex, currently only has data for reversal of intra-operative administration of non-depolarizing NMBAs.

## LITERATURE REVIEW

The clinical practice guidelines developed by the American College of Critical Care Medicine of the Society of Critical Care Medicine and updated in 2016, provide a detailed review of issues related to the sustained use of NMBAs in critically ill patients (2). The physiology of the neuromuscular receptor and pharmacology of NMBAs used in the ICU setting are reviewed. Additionally, methods for patient monitoring as well as side-effects are discussed, and recommendations are given. An evidence-based review focusing on the use of NMBAs in critically ill septic patients provides recommendations specific to this population (3).

Selected studies addressing indications, monitoring and complications are discussed below.

### Indications

#### *Individual & Short-Term Dosing*

NMBAs have multiple uses in an ICU setting. Individual dosing of NMBAs can be used for procedures, rapid sequence intubation, central line placement, tracheostomy, and dressing changes. Indications for short-term use include transport between departments or facilities to provide an element of safety during patient movement.

#### *Acute Respiratory Distress Syndrome*

Invasive mechanical ventilation remains the cornerstone of treatment for acute respiratory distress syndrome (ARDS). Invasive ventilation involves the use of sedation to allow for patient comfort while on the ventilator. In some cases, however, the use of sedation is not sufficient and other adjunct methods are needed. According to a review article by Bourene et al. approximately 25-45% of ARDS patients require NMBAs for an average of  $1 \pm 2$  days and the main indications for initiating are hypoxemia and need for mechanical ventilation (4). In 2016, Murray et al. recommended a short course (< 48 hours) of paralysis for patients with moderate to severe ARDS ( $\text{PaO}_2/\text{FiO}_2$  ratio < 150) (2,4). In 2017, the Surviving Sepsis Campaign also recommended a trial of NMBA therapy for severe ARDS (4). A randomized controlled trial by Gannier, et al. demonstrated the benefit of NMBAs (primarily with cisatracurium) on oxygenation for patients with moderate to severe ARDS (5,6)

### *Intraabdominal Hypertension*

NMBAs can be used as medical management strategy for preventing abdominal compartment syndrome and ultimately decompressive laparotomy for those patients with elevated intra-abdominal pressures through the reduction of abdominal wall muscle tone (7).

### *Elevated Intracranial Pressures*

NMBAs may be used to help control persistently elevated intracranial pressures in patients with traumatic brain injury. NMBAs can either prevent or decrease the sympathetic and reflex response to tracheal suctioning which would otherwise elevate intracranial pressure (1). NMBAs help to facilitate mechanical ventilation (carbon dioxide elimination, lower positive end-expiratory pressure), decrease metabolic expenditure, and limit elevations in intracranial pressure after stimulating procedures. (6) They can also decrease respiratory drive and intra-abdominal pressure, thus improving cerebral flow both towards and away from the brain. The use of NMBAs in traumatic brain injury has not been demonstrated to improve long-term patient outcomes however.

### *Therapeutic Hypothermia after Cardiac Arrest*

NMBAs can be used to decrease shivering associated with therapeutic hypothermia. Shivering leads to heat production, inflammation, elevated intracranial pressure, decreased brain tissue oxygen levels, and increased metabolic rate. Many studies are retrospective and show conflicting data on increased survival rates and complications, thus prompting the American Heart Association guidelines to recommend avoidance or minimal use of NMBAs (6).

### Monitoring

NMBAs should be preceded by appropriate sedation and analgesia prior to initiation of pharmacologic paralysis. NMBAs drugs should be titrated to the lowest effective dose to maintain treatment paralysis. It is important to note that paralysis can be difficult to control because of changing body temperature, changes in muscle blood flow, altered electrolytes, and use of various medications (1).

A prospective, randomized, controlled investigation was conducted in 77 critically ill medical patients to compare outcomes between two different monitoring methods of neuromuscular blockade (8). 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 housestaff were blinded to the results and made dosage adjustments 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 was 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 (Class I).

In another trial, medical ICU patients receiving continuous cisatracurium were randomized to TOF monitoring (n=16) or clinical assessment (n=14) (9). Clinical assessment consisted of adjusting the NMBA based on observed responses of the patient. Specifically, nurses monitored for 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). 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. Additionally, no cases of prolonged paralysis syndrome or clinical evidence of acute myopathy were noted (Class I)

Side-effects

There is an increasing body of literature reporting prolonged neuromuscular dysfunction following the use of NMBAs. This can result from either drug accumulation or the development of acute quadriplegic myopathy syndrome (AQMS). AQMS includes critical illness myopathy, myopathy with selective loss of thick (myosin) filaments, and acute necrotizing myopathy of intensive care (10). It is characterized by acute paresis, myonecrosis, and abnormal electromyography findings (2). Sensory function generally remains intact. A number of factors have been reported to potentiate the development of prolonged neuromuscular dysfunction, most notably the concomitant use of corticosteroids. Although most reports describe the use of high-dose corticosteroids in combination with a steroid-based NMBA, the benzylisoquinolinium agents have also been implicated (11). One mechanism responsible for this drug interaction is an additive decrease in thick filament proteins (12).

Other side-effects of prolonged NMBAs use include drug toxicity; increased venous thromboembolism events; medication interactions; hemodynamic, autonomic and other physiologic responses; corneal injury; vision loss; skin breakdown; decreased gastrointestinal motility; diaphragmatic atrophy; and peripheral muscle weakness. Table 2 provides a list of medications that may affect neuromuscular blockade when used in combination with NMBAs (14,15).

**TABLE 1: Medications affecting neuromuscular blocker activity**

<b>Potentiate</b>	<b>Antagonize</b>
Antiarrhythmics: procainamide, quinidine, verapamil	Antiepileptics: carbamazepine, phenytoin
Antibiotics: aminoglycosides, tetracyclines, clindamycin	Other: ranitidine, theophylline
Cardiovascular medications; Beta-blockers, Calcium channel blockers	
Cations: calcium, magnesium	
Immunosuppressants: cyclophosphamide, cyclosporine	
Inhaled anesthetics: desflurane, sevoflurane, isoflurane, halothane	
Local anesthetics	
Other: dantrolene, diuretics, lithium	

**TABLE 2. Overview of various NMBA's (2, 6, 14-15)**

	Depolarizing Agent	AMINOSTEROIDAL AGENTS			BENZYLISOQUINOLINIUM AGENT	
NMBA	Succinylcholine	Pancuronium (Pavulon®)	Rocuronium (Zemuron®)	Vecuronium (Norcuron®)	Cisatracurium (Nimbex®)	Atracurium (Tracrium®)
Initial dose (mg/kg)	1.5	0.06-0.1	0.6-1.2	0.08-0.1	0.1-0.2	0.4-0.5
Onset (s)	30-60		65-90			120-180
Duration (min)	10	90-100	25-50	35-45	45-60	20-35
Infusion dose (µg/kg/min)	Not recommended	1-2	0.5-2	0.8-1.2	2.5-3	5-20
Recovery (min)	5-10 min	120-180	55-160	45-60	90	
% Renal excretion	Metabolism is via Plasma Cholinesterase	45-70	30-50	50	Hoffman elimination	Hoffman elimination
Renal failure		Increased effect	Increased duration	Increased effect	No change	No change
% Biliary excretion		10-15	50-70	35-50	Hoffman elimination	Hoffman elimination
Hepatic failure		Mild increased effect	Moderate	Variable, mild increased effect	Minimal to no change	Minimal to no change
Active metabolites	No	Yes	No	Yes	No	Yes
Histamine release (hypotension)	Yes	No	No	No	No	Yes
Vagal block (tachycardia)	N/A	Modest to marked	No; Could be some at higher doses	No	No	No
Prolonged ICU block	N/A	Yes	No	Yes	Rare	Rare
Evidence for critical illness polyneuromyopathy	N/A	+++	+++	+	+	+
Relative Cost	\$	\$	\$\$	\$\$	\$\$\$	\$\$\$\$

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