

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

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**
 - **Systemic use of NMBAs in early management of ARDS patients improves oxygenation.**
- **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].**
 - **NMBA therapy can be used for a short course (<48 hours) of paralysis in patients with severe ARDS (PaO₂/FiO₂ ratio <150).**
- **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**
 - **Cisatracurium is the NMBA of choice for renal and hepatic impaired patients. Although, rocuronium is primarily used at our institution.**
 - **In patients able to tolerate interruption of neuromuscular blockade, the NMBA infusion should be interrupted daily to assess motor function and level of sedation.**
 - **Physical therapy should be provided to patients on NMBAs.**

SUMMARY

Although NMBAs may be used to facilitate mechanical ventilation and treat muscle contractures associated with tetanus, the scientific support is limited. There has been recent randomized control trials which have demonstrated benefit in patients with acute respiratory distress syndrome. NMBAs do appear to be beneficial in post-cardiac arrest therapeutic hypothermia and medical management of intra-abdominal hypertension after other methods have failed. Due to the lack of data supporting improved long-term outcomes for other indications, as well as the potential for serious adverse effects, the use of these agents should be reserved for select clinical situations. Several guidelines suggest NMBAs only be used when all other modalities have been exhausted. Given that concomitant medications and

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.

comorbidities commonly preclude the use of aminosteroidal agents in the surgical critical care population, cisatracurium is considered our NMBA of choice despite its higher cost. Although, rocuronium is primarily used at our institution in patients with renal failure. Several adjunctive therapies are necessary in the paralyzed patient and must not be overlooked.

INTRODUCTION

Neuromuscular blocking agents (NMBAs) should be considered an intervention of last resort due to the multiple complications 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 Ach, 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 they act as competitive antagonists. Non-depolarizing NMBAs have either an aminosteroidal or benzylisoquinolinium 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 complete overview of various NMBAs used commonly in clinical practice.

NMBAs infusion are discontinued to allow muscular function to gradually recover as NMBAs are metabolized and eliminated. If rapid reversal is required, then anticholinesterase agents (edrophonium, neostigmine, pyridostigmine) with antimuscarinic agents (glycopyrrolate, atropine) can be used.

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, provides 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 of monitoring and complications are discussed, and recommendations are provided. 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 intensive care setting. Individual dosing of NMBAs can be used for procedures, rapid sequence intubation, central line placement, tracheostomy, and dressing changes. Whereas, short term use includes 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 NMBA for an average of 1 ± 2 days and the main indications for initiating are hypoxemia and need for mechanical ventilation (4). In 2016, the clinical guidelines by Murray et al, recommended a short course (<48 hours) of paralysis for patients with severe ARDS (PaO₂/FiO₂ 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 NMBA (primarily with cisatracurium) on oxygenation for patients with moderate to severe ARDS (5). (15)

Intraabdominal Hypertension

NMBA can be used as medical management strategy for preventing abdominal compartment syndrome and ultimately decompressive laparotomy for those patients with elevated intraabdominal pressures (6). NMBA reduce abdominal wall muscle tone

Elevated Intracranial Pressures

NMBA are used to help control persistently elevated intracranial pressures in patients with head trauma. NMBA can either prevent or decrease the sympathetic and reflex response to tracheal suctioning which would otherwise elevate intracranial pressure (1). NMBA help to facilitate mechanical ventilation (carbon dioxide elimination, lower positive end expiratory pressure), decrease metabolic expenditure, and limit elevations in intracranial pressures after stimulating procedures. (15) They also can decrease the respiratory drive and intraabdominal pressures thus help to improve cerebral flow both towards and away from the brain. The use of NMBA in traumatic brain injury has not demonstrated improved outcomes.

Therapeutic Hypothermia after Cardiac Arrest

NMBA can be used to decrease shivering which is consequence of 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 NMBA (15).

Monitoring

Patients in whom NMBA are used on for treatment of various conditions are often profoundly critically ill. NMBA should be preceded by appropriate sedation and analgesia prior to initiation of paralysis. NMBA 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 (7). 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 4/4 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. (Class I)

In another trial, medical ICU patients receiving continuous cisatracurium were randomized to TOF monitoring (n=16) or clinical assessment (n=14) (8). 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)

Complications

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 (9). 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 (10). One mechanism responsible for this drug interaction is an additive decrease in thick filament proteins (11).

Other complications associated with prolonged use of NMBAs include drug toxicity, increased risk of 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 (13,14).

Potentiate	Antagonize
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 1. Medications affecting neuromuscular blocker activity

	Depolarizing Agent	AMINOSTEROIDAL AGENTS			BENZYLISOQUINOLIUM 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	\$	\$	\$\$	\$\$	\$\$\$	\$\$\$\$

Table 2. Overview of various NMBAs (2, 13-15)

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