NEUROMUSCULAR BLOCKING AGENTS (NMBAs) IN ADULT INTENSIVE CARE UNITS

RECOMMENDATIONS

- **Patients MUST be mechanically ventilated prior to administration of NMBAs.**
- **Adequate sedative and analgesic therapy MUST be provided prior to and for the duration of neuromuscular blockade.**
- **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].**
- **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 our NMBA of choice.**
  - **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 to case studies and small trials. 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 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. In fact, recent Surviving Sepsis Campaign Guideline have advocated for the avoidance of NMBAs if at all possible. Given that concomitant medications and 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. A number of adjunctive therapies are necessary in the paralyzed patient and must not be overlooked.

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.

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INTRODUCTION

Neuromuscular blocking agents (NMBAs) should be considered an intervention of last resort due to the multiple complications associated with their use. These agents are classified based upon their structure, mechanism of action, and pharmacokinetic properties. Structurally, NMBAs have either an aminosteroidal or benzylisoquinolinium nucleus. 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. Non-depolarizing agents also bind to acetylcholine receptors, but instead of activating them they act as competitive antagonists. 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.

	AMINOSTEROIDAL AGENTS		**BENZYLISOQUINOLINIUM AGENT**
NMBA	**Pancuronium (Pavulon®)**	**Vecuronium (Norcuron®)**	**Cisatracurium (Nimbex®)**
Initial dose (mg/kg)	0.06-0.1	0.08-0.1	0.1-0.2
Duration (min)	90-100	35-45	45-60
Infusion dose (μg/kg/min)	1-2	0.8-1.2	2.5-3
Recovery (min)	120-180	45-60	90
% Renal excretion	45-70	50	Hoffman elimination
Renal failure	Increased effect	Increased effect	No change
% Biliary excretion	10-15	35-50	Hoffman elimination
Hepatic failure	Mild increased effect	Variable, mild increased effect	Minimal to no change
Active metabolites	Yes	Yes	No
Histamine release (hypotension)	No	No	No
Vagal block (tachycardia)	Modest to marked	No	No
Prolonged ICU block	Yes	Yes	Rare
Relative Cost	$	$$	$$$

Adapted from Murray et al. *Crit Care Med* 2002; 30:142-56

LITERATURE REVIEW

The clinical practice guidelines developed by the American College of Critical Care Medicine of the Society of Critical Care Medicine provide a detailed review of issues related to the sustained use of NMBAs in critically ill patients (1). 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 (2).

Selected studies addressing monitoring and complications are discussed below.

Monitoring

A prospective, randomized, controlled investigation was conducted in 77 critically ill medical patients to compare outcomes between two different monitoring methods of neuromuscular blockade (3). 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) (4). 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 (5). It is characterized by acute paresis, myonecrosis, and abnormal electromyography findings (1). 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 (6). One mechanism responsible for this drug interaction is an additive decrease in thick filament proteins (7). The following table provides a list of antibiotics that may potentiate neuromuscular blockade when used in combination with NMBAs.

ANTIBIOTICS THAT MAY ENHANCE THE EFFECTS OF NONDEPOLARIZING NMBAs
• Aminoglycosides
• Clindamycin
• Polymyxins
• Colistin
• Tetracyclines

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