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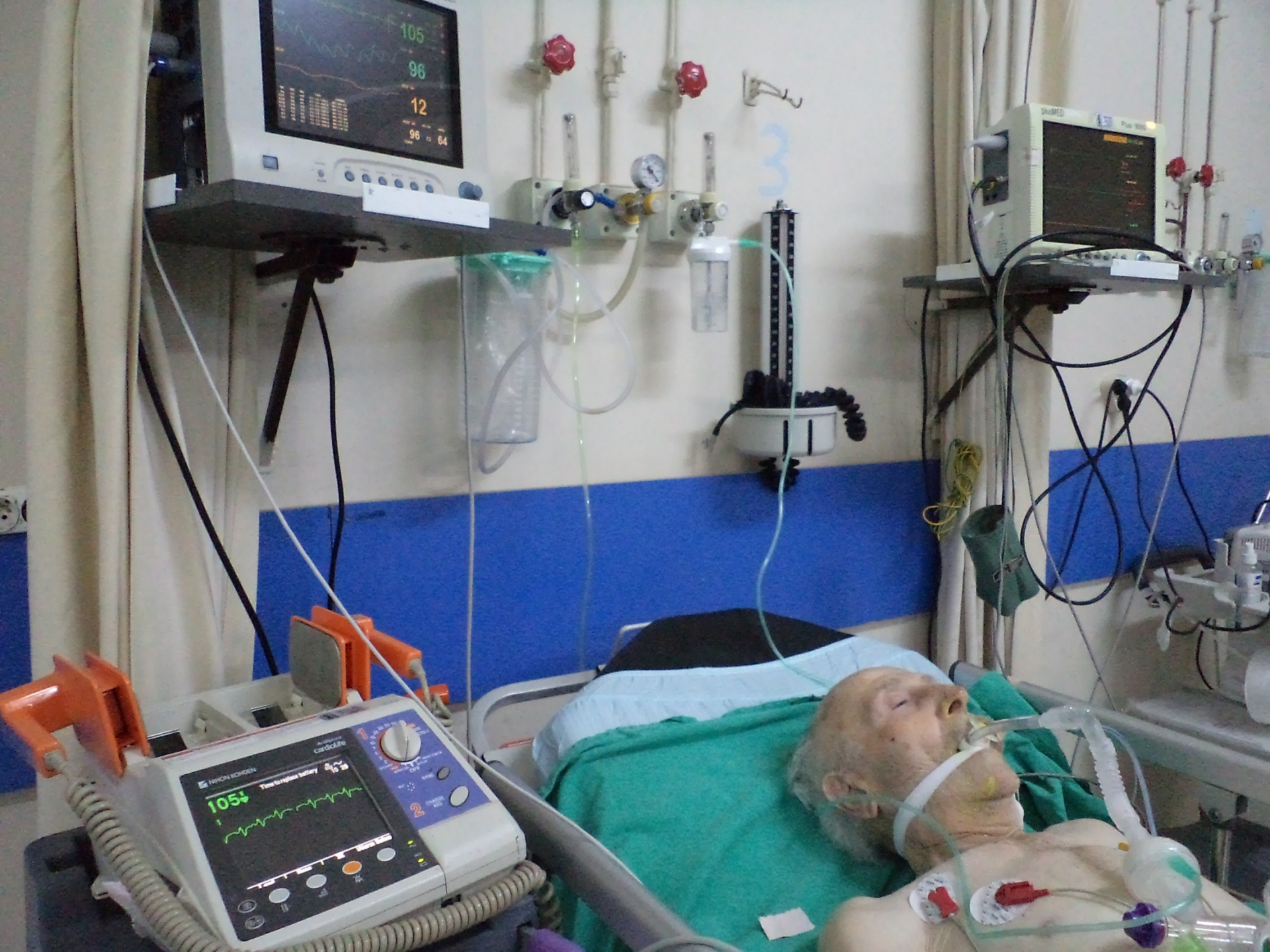
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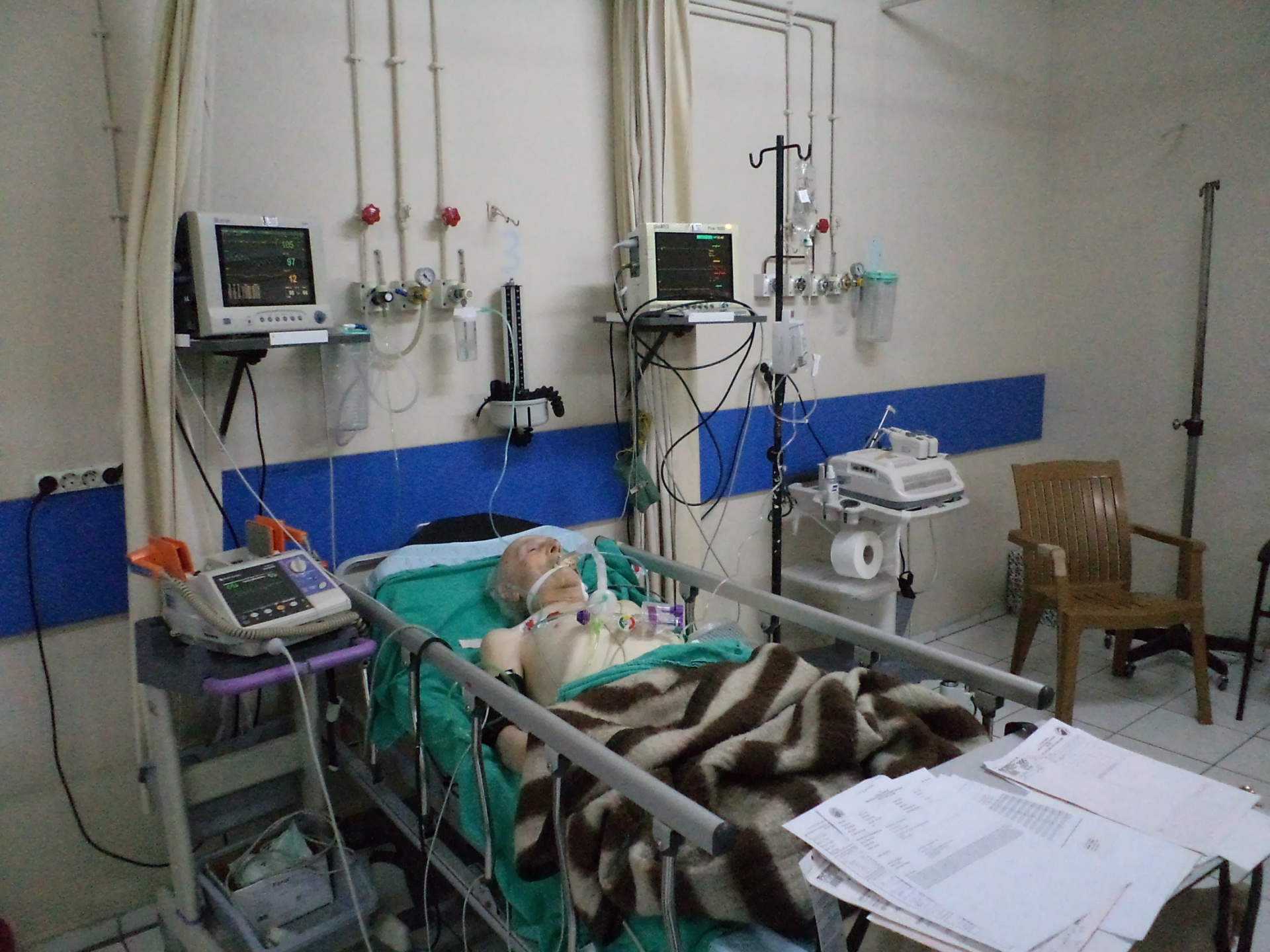


HÔPITAL RÉGIONAL DE SUDBURY REGIONAL HOSPITAL

TRAIN OF FOUR MONITORING

Self Learning Program

Physiology of Neuromuscular Transmission:

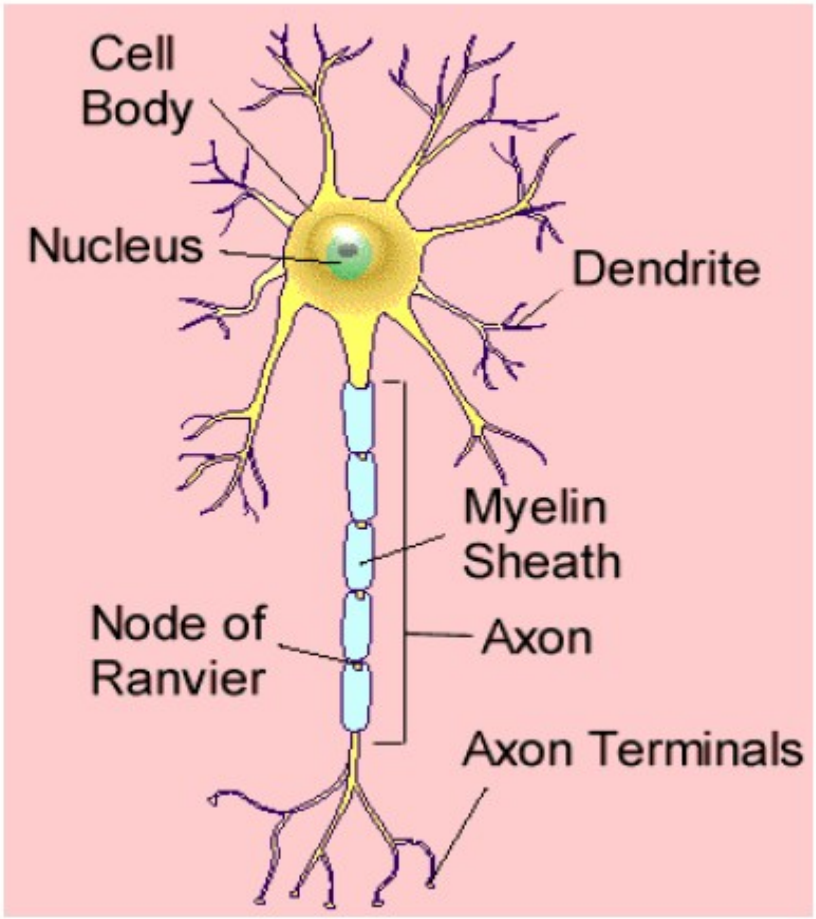
- Electrical impulses generated by neurons that originate from the central nervous system are responsible for muscle contraction.

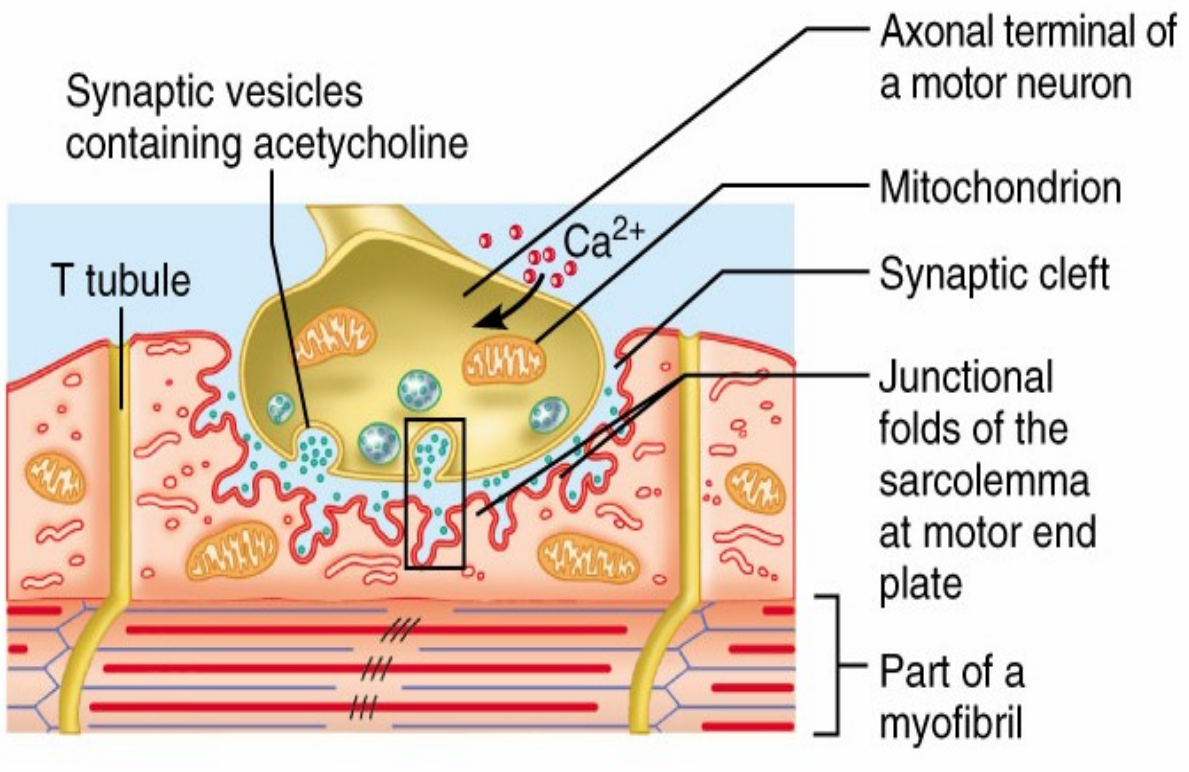
- These electrical impulses are called “action potentials”.

- Electrical impulses travel down the body of neurons (axons) that conduct and transmit

The synapse, or connection, of this engagement is called the **neuromuscular junction**.

MOTOR NEURON





(b)

Indications for use of NMBA's in the critical care setting:

- ✓ To facilitate endotracheal intubation under special circumstance (not for residents)

  Rationale: Relaxation of laryngeal muscles facilitates passage of endotracheal tube

- ✓ To facilitate mechanical ventilation and improve gas exchange in patients who cannot be managed with sedation, analgesia and ventilator parameter manipulation alone (i.e., poor lung and chest wall compliance)

  Rationale: High levels of PEEP, prolongued inspiratory time, inverse I:E ratio are uncomfortable for patients resulting in asynchrony between patient and ventilator thus the need for relaxation of respiratory muscles.

- ✓ For struggling, "bucking", coughing or hiccupping despite adequate sedation

  Rationale: Asynchronous breathing results causing poor oxygen saturation and increase risk of barotrauma thus the need for relaxation of respiratory muscles.

- ✓ To reduce intracranial pressure (ICP) peaks which may occur with muscular effort in the patient with elevated ICP

  Rationale: Paralysis lowers ICP which prevents decreased CPP resulting in increased perfusion to brain

- ✓ To transiently control excessive shivering

  Rationale: Prevent an increase in oxygen consumption, hypercarbia

- ✓ For inappropriate, insuppressible respirations ie: central neurogenic hyperventilation

  Rationale: Asynchronous breathing results causing poor oxygen saturation and increase risk of barotrauma thus the need for relaxation of respiratory muscles.

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.**

Surgical Critical Care Evidence-Based Medicine Guidelines Committee

Primary Reviewer: Joseph Ibrahim, MD
Editor: Michael L. Cheatham, MD
Last revision date: September 1, 2012

Please direct any questions or concerns to: mailto:webmaster@surgicalcriticalcare.net

REVIEW Open Access

A fresh look at paralytics in the critically ill: real promise and real concern

David Price[2], Nicholas J Kenyon[1,2] and Nicholas Stollenwerk[1,2*]

- Neuromuscular blocking agents (NMBAs), or "paralytics," often are deployed in the sickest patients in the intensive care unit (ICU) when usual care fails.
- Despite the publication of guidelines on the use of NMBAs in the ICU in 2002, clinicians have needed more direction to determine which patients would benefit from NMBAs and which patients would be harmed.

REVIEW Open Access

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David Price[2], Nicholas J Kenyon[1,2] and Nicholas Stollenwerk[1,2*]

- ***Recently, new evidence has shown that paralytics hold more promise when used in carefully selected lung injury patients for brief periods of time.***

- When used in early acute respiratory distress syndrome (ARDS), NMBAs assist to establish a lung protective strategy, which leads to improved oxygenation, decreased pulmonary and systemic inflammation, and potentially

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- ***Ultimately***;

- We conclude that NMBAs should be considered a lung protective adjuvant in early ARDS and that clinicians should consider using an alternative NMBA to the aminosteroids in septic shock with less severe lung injury pending further studies.

Review of Common Neuromuscular Blocking Agents:

Diagram #3

DRUG	TYPE	ROUTE OF ELIMINATION	ONSET OF ACTION	DURATION OF ACTION	ADVERSE EFFECTS
Succinylcholine (Quelicin)	Depolarizing	Plasma cholinesterase	30-60sec	4-6 min	Hyperkalemia, increased intragastric/ intraocular/ intracranial pressures, malignant hyperthermia, hypotension, bradycardia
Rocuronuim (Zemuron)	Non-Depolarizing	Hepatic and renal	30-60sec	30 min	Hypo/hypertension, arrhythmia, rash
Pancuronuium (Pavulon)	Non-Depolarizing	Renal and hepatic	2-3min	60-100 min	Tachycardia, hypo/hypertension, bronchospasm, rash
Cisatricurium (Nimbex) ***Light sensitive***	Non-Depolarizing	Hoffman degradation	2-3min	25-45 min	Hemodynamic instability, bronchospasm, rash

Contraindications to use of NMBA's and peripheral nerve stimulation:

Contraindication	Rationale
• NO advanced airway in place	• Cessation of respiration will cause patient to die
• CPAP mode	• Ventilator must be set on mode with rate in order for paralyzed patient to be ventilated
• Inability to administer sedation	• Minimize potential for post-traumatic stress syndrome
• Unstable bone fractures	• Loose bony fragments may further damage surrounding tissues, organs, and blood vessels if the muscles surrounding the fragments relax.
• Lack of knowledge regarding potential complications	• Patient at risk for development of complications if staff unaware of risks

Factors that alter neuromuscular blockade

Factors that alter neuromuscular blockade:

- ✓ Calcium channel blockers
- ✓ Corticosteroids
- ✓ Diuretics (furosemide and thiazides)
- ✓ Carbemazapine
- ✓ Enflurane and isoflurane (inhalants)
- ✓ Antibiotics (amikacin, clindamycin, gentamycin, kanamycin, neomycin, pipercillin, plymyxin A,B and E, streptomycin, tetracyclines and tobramycin)
- ✓ Anti arrhythmic medications (bretyllium, lidocaine, propranolol, quinidine)
- ✓ Electrolyte and thermal disorders (hypokalemia, hypocalcemia, hypomagnesemia, hyponatremia, hypothermia, acidosis)
- ✓ Organ failure (renal and hepatic)
- ✓ Neuromuscular diseases

Nursing care and considerations (cont'd):

- Initiate pressure ulcer prevention techniques ie: repositioning, skin care measures….
  - Complete ulcer risk assessment record
  - Place patient on pressure relief/reduction mattress
  - Reposition patient q2h and prn in correct anatomical alignment
- Regular tracheal suctioning as required
- Answer all ventilator alarms promptly, continuous SaO_2 monitoring, draw ABG's as ordered
- Keep bag-valve-mask and airway at beside for emergency (displacement of endotracheal tube or mechanical dysfunction)
- q1h monitoring of vital signs unless more frequently required – some NMBA's cause increased or decreased heart rates, hypotension, hyperthermia (which may cause a rare hypermetabolic condition called "malignant hyperthermia"), hypothermia (which may prolong the effect of the NMBA)
- Pupillary assessment q4h minimum during paralysis
- Visual and clinical assessment of the patient's response to NMBA should be performed in conjunction with TOF monitoring ie. Tactile assessment of patients muscle tone, skeletal muscle movement and respiratory effort.
- Once paralytics discontinued, maintain sedation until TOF reaches 4/4 twitches

Table 1 Clinical pharmacology of nondepolarizing neuromuscular blocking agents

NMBA	Peak effect (min)	Recovery (min)	Metabolism	Renal elimination (%)	Biliary elimination (%)	Vagolytic effect	Histamine release	Critical illness polyneuromyopathy
Benzylisoquinolinium								
Atracurium	2-3	30-60	Hoffman Elimination (blood)	5-10	None	None	+	+
Cisatracurium	1-7	40-90		None	None	None	None	+
Aminosteroid								
Pancuronium	2-3	80-180	Liver	40-70	10-15	+++	None	+++
Rocuronium	1-2	20-60		10-30	50-75	+	None	+
Vecuroniurn	2-3	40-60		15-50	35-50	None	None	+++

+ minimal, ++ moderate, +++ marked.

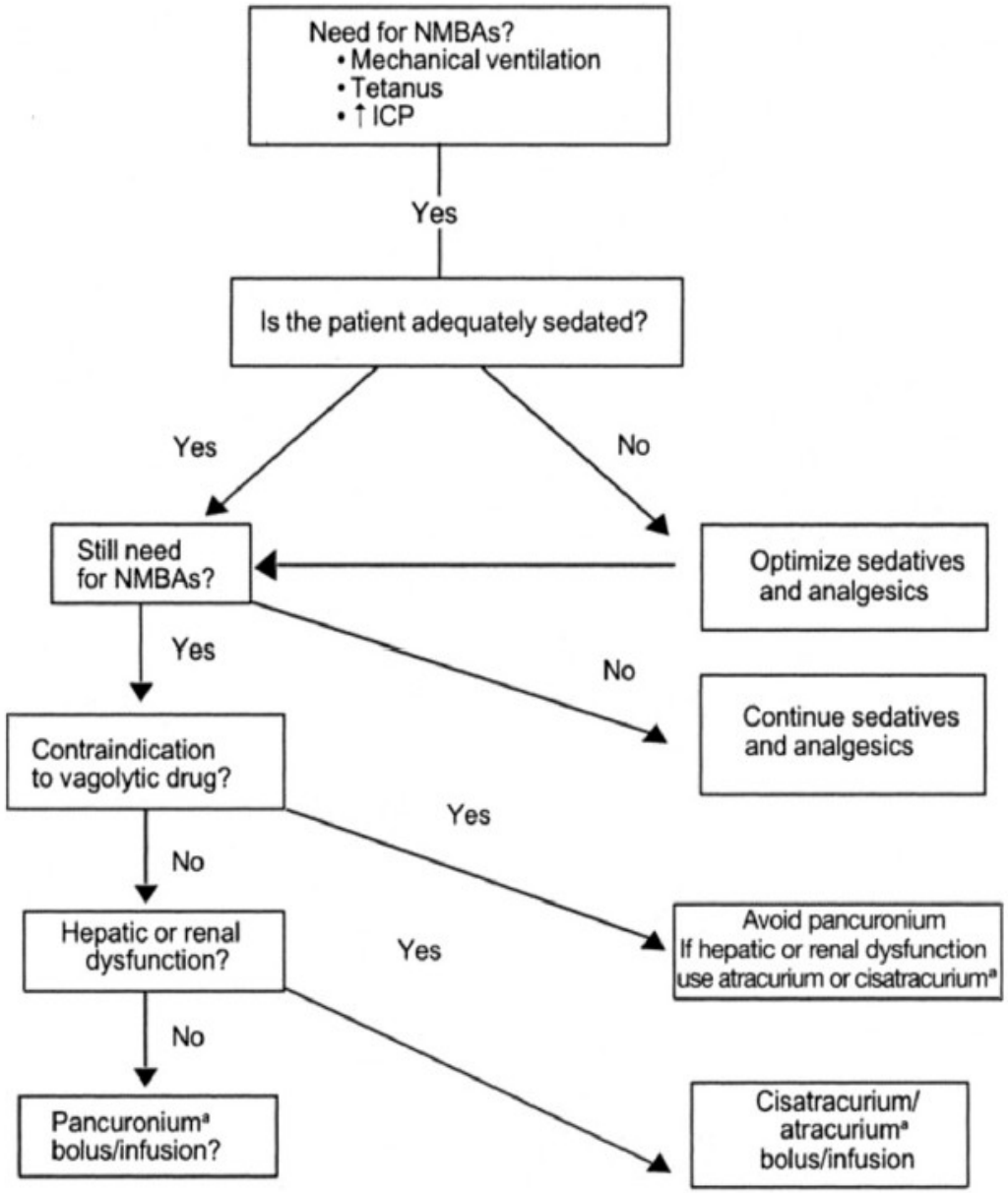

Figure 1 Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Reprint with permission from [1].

Table 2 Studies of NMBAs related to prolonged weakness, CIP, and CIM

NMBA	Author	Subjects	Study design	Motor	Sensory	EMG	Muscle biopsy	Prolonged weakness, CIP, and CIM
Benzylisoquinolinium								
Cisatracurium								
Human studies								
	Fodale et al. [36]	1	Case report	Y	N	Y	N	NMBA and CS for 7 days in patient with chest wall trauma led to quadriplegia consistent with CIM.
	Davis et al. [35]	1	Case report	Y	N	N	N	NMBA and CS for 6 days with 6 additional days of NMBA in 45-year-old with ARDS led to CIM.
Atracurium								
Human studies								
	Tousignant et. al. [38]	1	Case report	Y	N	Y	N	18-year-old asthmatic with 7 days of NMBA and CS develops acute quadriparesis 3 days after cessation of NMBA consistent with CIM.
	Meyer et al. [37]	2	Case report	Y	N	Y	N	38-year-old receiving CS and 8 days of NMBA developed CIM. 25-year-old with good pastures receiving CS and NMBA for 6 days develop CIM.
Aminosteriods								
Pancuronium								
Human studies								
	Behbehani et al. [26]	86	Retrospective Cohort	Y	N	Y	N	Asthmatics receiving NMBA and CS. Pancuronium, vecuronium used in 30 with 9 developing CIM. All nine received pancuronium.
	de Lemos et al. [39]	30	Prospective Observational Cohort	Y	N	Y	N	Study of recovery time in continuous infusion versus bolus groups. Six patients with CIM, five of which received continuous infusion. No statistical difference in total dose between groups.
	Giostra et al. [30]	9	Prospective Cohort	Y	Y	Y	Y	Over 2 years, nine patients with respiratory failure requiring mechanical ventilation and NMBA developed CIP. Eight of nine received concomitant NMBA and CS.
Rocuronium								
Animal Studies								
	Maes *et al.* [40]	Rat / 27	Prospective Randomize	N/A	N/A	Y	Y	1 dose of CS added to 24 hours of NMBA results in decreased CIM of diaphragm than NMBA alone.
	Testelmans *et al.* [33]	Rat / 24	Prospective Randomize	N/A	N/A	Y	Y	24 hours of rocuronium associated with worse CIM than cisatracurium.
	Testelmans *et al.* [32]	Rat / 34	Prospective Randomize	N/A	N/A	Y	Y	24 hours of NMBA associated with increased CIM than mechanical ventilation alone.
Vecuronium								
Human Studies								
	Garnacho-Montero *et al.* [25]	73	Prospective Cohort	Y	Y	Y	N	In septic cohort with more than 2 organ failure, 9 of 10 patients who got NMBA developed CIP. 6 received vecuronium and 3 received atracurium
	Rudis *et al.* [34]	77	Prospective Randomized Single-Blind	Y	N	Y	N	Use of peripheral nerve stimulator resulted in half dose of NMBA given. 16 patients with prolonged blockade and 4

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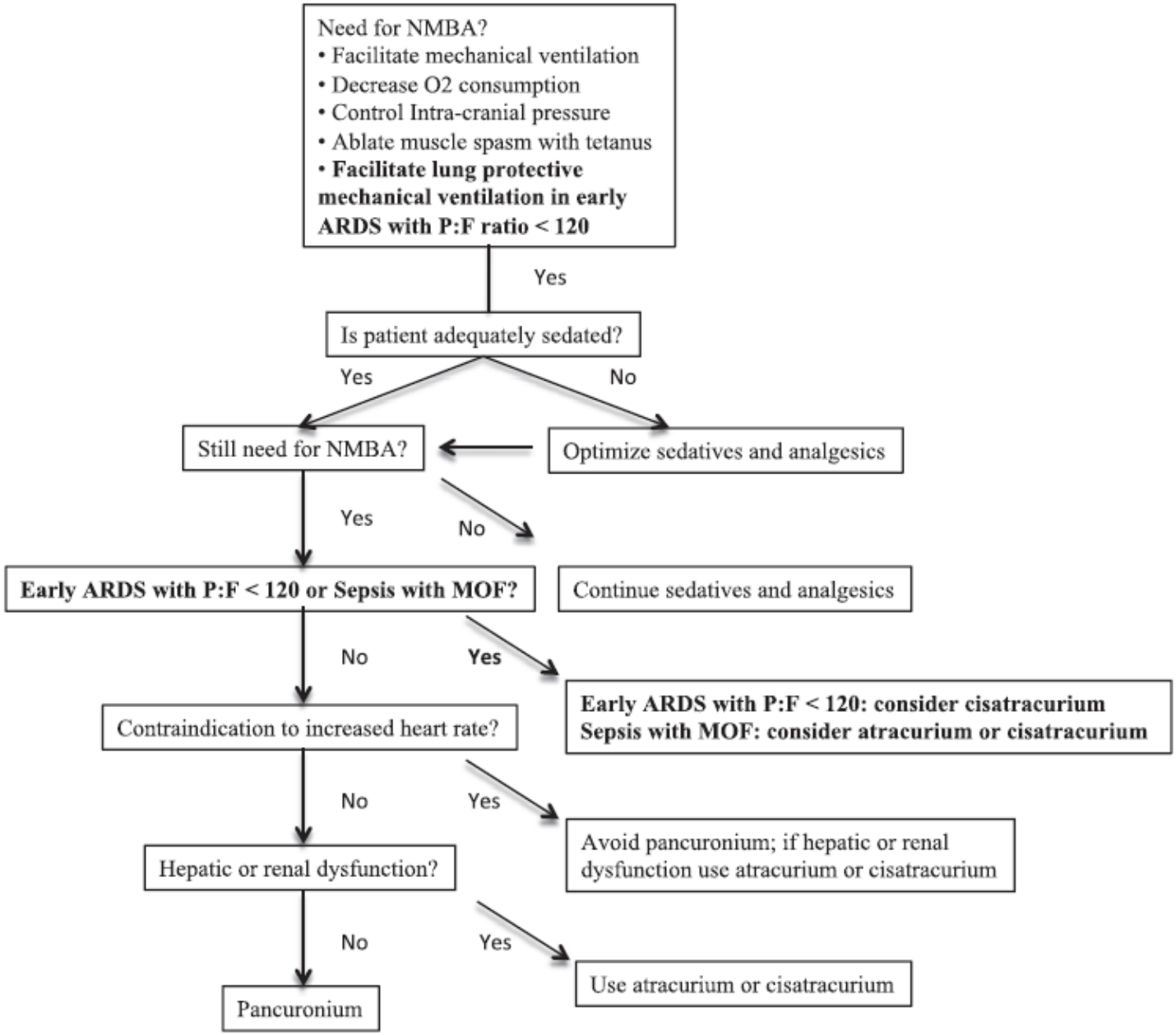
Table 2 Studies of NMBAs related to prolonged weakness, CIP, and CIM *(Continued)*

							with CIP. More prolonged blockade and CIP in group with more NMBA.
Prielipp *et al.* [41]	58	Prospective Randomized Double-Blind	Y	Y	Y	Y	Prolonged recovery in 13 patients with vecuronuim versus 2 with cisatracurium (p=0.002). CIP in 1 vecuronuim patient.
Douglass *et al.* [27]	25	Prospective Cohort	Y	N	N	N	22 patients received NMBA and CS. 9 developed CIM. CIM associated with time ventilated and dose of NMBA received.
Kupfer *et al.* [31]	28	Prospective Cohort	Y	1/5	Y	N	50% of patient without sepsis or multi-organ failure with more than 6 hours of NMBA infusion developed weakness. 1 CIPM, 4 CIM. CIPM and CIM ssociate with increase dose.
Danon *et al.* [42]	1	Case report	Y	N	N	Y	20 year old asthmatic who received CS and NMBA for 10 days developed CIM.

Y, yes; N, no; N/O, not obtained; CS, corticosteroid; CIP, critical illness polyneuropathy; CIM, critical illness myopathy; CIPM, critical illness polyneuromyopathy; NMBA, neuromuscular blocking agent; ARDS, acute respiratory distress syndrome [25-27,30-38,44-48]

Figure 2 Suggested modifications to clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient

Bolded text represents suggested modifications to 2002 guidelines.



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.

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.

These agents are classified based upon their structure, mechanism of action, and pharmacokinetic properties or Mechanistically, they are classified as either depolarizing or non-depolarizing

	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

Which used to NMBA

- 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

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.

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

Monitoring

- Overall, 71% of patients (including patients from both groups) had abnormal neurologic

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***

Annals of Intensive Care
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RESEARCH Open Access

Neuromuscular blocking agents in patients with acute respiratory distress syndrome: a summary of the current evidence from three randomized controlled trials

Ary Serpa Neto[1*], Victor Galvão Moura Pereira[1], Daniel Crepaldi Espósito[1], Maria Cecília Toledo Damasceno[1] and Marcus J Schultz[2]

Abstract

Background: Acute respiratory distress syndrome (ARDS) is a potentially fatal disease with high mortality. Our aim was to summarize the current evidence for use of neuromuscular blocking agents (NMBA) in the early phase of ARDS.

Methods: Systematic review and meta-analysis of publications between 1966 and 2012. The Medline and CENTRAL databases were searched for studies on NMBA in patients with ARDS. The meta-analysis was limited to: 1) randomized controlled trials; 02) adult human patients with ARDS or acute lung injury; and 03) use of any NMBA in one arm of the study compared with another arm without NMBA. The outcomes assessed were: overall mortality, ventilator-free days, time of mechanical ventilation, adverse events, changes in gas exchange, in ventilator settings, and in respiratory mechanics.

Results: Three randomized controlled trials covering 431 participants were included. Patients treated with NMBA showed less mortality (Risk ratio, 0.71 [95 % CI, 0.55 – 0.90]; number needed to treat, 1 – 7), more ventilator free days at day 28 ($p = 0.020$), higher PaO_2 to FiO_2 ratios ($p = 0.004$), and less barotraumas ($p = 0.030$). The incidence of critical illness neuromyopathy was similar ($p = 0.540$).

Conclusions: The use of NMBA in the early phase of ARDS improves outcome.

Keywords: ARDS, Neuromuscular blocking agents, Meta-analysis, Review

- Acute respiratory distress syndrome (ARDS) is a common and life-threatening condition that complicates a variety of critical illnesses, including sepsis, pneumonia, and trauma

- Characterized by intense lung inflammation, consolidation, and progressive microatelectasis, ARDS is associated clinically with severe hypoxemia, patient-ventilator dyssynchrony, and high susceptibility to

Neuromuscular blocking agents are used in the ICU setting for 3 reasons

- To eliminate spontaneous breathing and Promote mechanical ventilation
- Cause a pharmacologic restraint so patients do not harm themselves
- To decrease oxygen consumption

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
- It is characterized by acute paresis, myonecrosis, and abnormal electromyography findings.
- 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.
- One mechanism responsible for this drug interaction is an additive decrease in thick filament proteins.

ANTIBIOTICS THAT MAY ENHANCE THE EFFECTS OF NONDEPOLARIZING NMBAs

- Aminoglycosides
- Clindamycin
- Polymyxins
- Colistin
- Tetracyclines

Alhazzani et al. Critical Care 2013, 17:R43
http://ccforum.com/content/17/2/R43

CRITICAL CARE

RESEARCH Open Access

Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials

Waleed Alhazzani[1*], Mohamed Alshahrani[2], Roman Jaeschke[1,3], Jean Marie Forel[4], Laurent Papazian[4], Jonathan Sevransky[5] and Maureen O Meade[1,3]

Abstract

Introduction: Randomized trials investigating neuromuscular blocking agents in adult acute respiratory distress syndrome (ARDS) have been inconclusive about effects on mortality, which is very high in this population. Uncertainty also exists about the associated risk of ICU-acquired weakness.

Methods: We conducted a systematic review and meta-analysis. We searched the Cochrane (Central) database, MEDLINE, EMBASE, ACP Journal Club, and clinical trial registries for randomized trials investigating survival effects of neuromuscular blocking agents in adults with ARDS. Two independent reviewers abstracted data and assessed methodologic quality. Primary study investigators provided additional unpublished data.

Results: Three trials (431 patients; 20 centers; all from the same research group in France) met inclusion criteria for this review. All trials assessed 48-hour infusions of cisatracurium besylate. Short-term infusion of cisatracurium besylate was associated with lower hospital mortality (RR, 0.72; 95% CI, 0.58 to 0.91; $P = 0.005$; $I^2 = 0$). This finding was robust on sensitivity analyses. Neuromuscular blockade was also associated with lower risk of barotrauma (RR, 0.43; 95% CI, 0.20 to 0.90; $P = 0.02$; $I^2 = 0$), but had no effect on the duration of mechanical ventilation among survivors (MD, 0.25 days; 95% CI, 5.48 to 5.99; $P = 0.93$; $I^2 = 49\%$), or the risk of ICU-acquired weakness (RR, 1.08; 95% CI, 0.83 to 1.41; $P = 0.57$; $I^2 = 0$). Primary studies lacked protracted measurements of weakness.

Conclusions: Short-term infusion of cisatracurium besylate reduces hospital mortality and barotrauma and does not appear to increase ICU-acquired weakness for critically ill adults with ARDS.