Neuromuscular Blocking Agents

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9.1 Introduction

Neuromuscular blocking agents (NMBAs) are widely used by anesthesiologists and intensivists in many clinical situations. Whereas in the operating room (OR), curarization is maintained for a limited period, in intensive care unit (ICU), it can last for days or weeks. In addition, the physiology of the critically ill patient is different from that of the ordinary surgical patient.

9.1.1 Sedation in ICU

Sedation is typically used in those patients who present agitation or anxiety due to pain, discomfort, hemodynamic instability, etc. Different levels of sedation can be achieved, from light (patient can be awakened) to deep (not arousable even with painful stimuli).

9.1.2 Neuromuscular Blockade in ICU

Neuromuscular blockade (NMB) in ICU is quite common (up to 13% of patients mechanically ventilated) and must be titrated on each patient according to clinical needs. Monitoring of NMB and an adequate sedation and analgesia are important to avoid adverse effects.

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A.R. De Gaudio, S. Romagnoli (eds.), *Critical Care Sedation*,
https://doi.org/10.1007/978-3-319-59312-8_9

9.2 Neuromuscular Transmission and Blockade

Movement, and also muscle trophism, is triggered by the interaction between motor neurons and muscle fibers. The contact point between these two structures is represented by the neuromuscular junction, where acetylcholine (ACh) is released from the presynaptic terminal to activate postsynaptic muscle-type nicotinic receptors, allowing the entry of Na + and Ca ++, and consequently the contraction.

There are also some presynaptic receptors, explaining the drug interaction with other medications:

- Nicotinic: stimulate the further release of ACh; their activation explains the train-of-four (TOF) fade with non-depolarizing blockers.
- Muscarinic: tend to be inhibitory receptors, reducing ACh release. Consequently, the administration of atropine will increase the release of ACh.
- α-Receptors: facilitate ACh release. In patients undergoing infusion of catecholamines, this could lead to a partial curarization.

NMBAs interfere with neuromuscular transmission: their use ranges from induction of anesthesia in ORs up to emergency intubation in ICU. They can also be used in critically ill patients, for example, to treat persistent shivering during therapeutic hypothermia or to improve the treatment of patients with ARDS. They are classically divided into depolarizing and non-depolarizing. The latter can be further divided according to their duration of action (long, intermediate, and short acting).

9.2.1 Depolarizing Agents

The only depolarizing agent used in clinical practice is succinylcholine: it is composed of two molecules of ACh linked by methyl groups. Although nicotinic receptor activation is similar to that caused by ACh, succinylcholine is not hydrolyzed by acetylcholinesterase of the synaptic cleft, resulting in prolonged depolarization. The block caused by this drug is divided into two phases:

- Phase I blockade (*depolarizing*): provokes a continuous firing from the motor neuron, often resulting in fasciculation. Succinylcholine seems to exert this action also with a prejunctional binding to nicotinic receptors, enhancing the neurotransmitter release.
- Phase II blockade: tends to appear with elevated plasma concentrations of succinylcholine or when it is administered in continuous infusion (even if at low doses, as in patients defective for plasmatic acetylcholinesterase). This block is characterized by a TOF response similar to that for the non-depolarizing agents. The causes seem to be (1) the maintenance of the resting potential following the activity of the Na^+ -K^+ ATPase and (2) the presynaptic blockade of ACh transport. Furthermore, desensitization can occur: ACh receptors become insensitive to the channel-opening effects of agonists.

Adult dose for intubation is 1–1.5 mg/Kg, with an onset of 60 s. Muscle relaxation lasts about 6 (2–10) min, with partial recovery already after 3 min.

The use of succinylcholine is not free from risks: various side effects can occur including muscle pain, tachycardia, bradycardia, ventricular arrhythmias, hypertension, hyperkalemia, and, less commonly, increased intracranial pressure or malignant hyperthermia (in patients with mutations of ryanodine receptor). The mean increase in K^+ is 0.5–1 mEq/L, which would be significant in patients with preexisting hyperkalemia. A special warning in the case of burn patients, following thermal injury, extra-junctional acetylcholine receptor expression increases in proportion to the magnitude of the burn. This results in an exaggerated release of potassium after administration of succinylcholine.

9.2.2 Non-depolarizing Agents

Non-depolarizing NMBAs exert their function on the postsynaptic side, antagonizing ACh in a competitive manner, preventing the conformational change in the receptor, or physically obstructing the ion channels so that an end plate potential is not generated. The non-depolarizing blockade is dynamic (binding and dissociation), so if ACh concentration increases, there is more chance of receptor binding compared to the antagonist. At least 92% of receptors must be occupied to obtain a complete block. Like succinylcholine, non-depolarizing NMBAs also exhibit desensitization block. An effect is also detected in prejunctional nicotinic receptors, resulting in failure of mobilization of ACh. Clinically, this is manifest as tetanic fade and TOF fade, in which there is a reduction in twitch height with successive stimuli. Non-depolarizing NMBAs are structurally divided into aminosteroid compounds (pancuronium, rocuronium, vecuronium) and benzylisoquinolines (atracurium, cisatracurium, mivacurium) [1].

Aminosteroids

These are formed of a steroidal skeleton with at least one quaternary ammonium group. Some deacetylated metabolites seem to exert a neuromuscular blockade.

Pancuronium is a long-acting compound with a long onset time (up to 3 min). It is metabolized in the liver in an active compound 3-hydroxypancuronium and then excreted in bile and urine. Although this drug does not release histamine, adverse effects can include tachycardia, hypertension, and increased cardiac output. These effects can partly counteract those of hypnotics administered for induction of anesthesia.

Vecuronium has an intermediate duration of action and onset time (2–2.5 min). It is metabolized by the liver to three active metabolites, all of which are excreted in urine. In patients with chronic kidney disease, this could lead to accumulation and prolongated NMB. Minimal adverse cardiovascular side effects have been reported.

Rocuronium is similar but less potent than vecuronium. It has a rapid onset (1–1.5 min) and short-to-intermediate duration of action, around 30–40 min. The drug is eliminated by the liver and the kidneys, and few adverse cardiovascular effects are reported. Rocuronium has no direct sympathomimetic effects but in high doses has a mild vagolytic property. Prolonged use, such as in ICU, causes a half-life extension.

Benzylisoquinolines

These are formed of two quaternary ammonium groups joined by a thin chain of methyl groups.

Atracurium is composed of ten stereoisomers: in fact, by selecting only a few of these, other benzylisoquinoline NMBAs are produced. The onset time is 1.5–2 min, while its action lasts for 35–43 min. The main metabolic pathways are represented by:

- Hofmann elimination (autolysis), pH and temperature dependent
- Non-specific esterases (hydrolysis)
- Renal excretion (of inactive metabolites)

No dosage adjustment is required in patients with hepatic or renal dysfunction. Moreover, according to the Hofmann reaction, acidosis and severe hypothermia decrease the rate of drug metabolism requiring dose adjustment, titrating according to patient's response. Atracurium causes histamine release, leading to hypotension; in addition to this, a sympathetic ganglionic blockade is present.

Cisatracurium is a single isomer of atracurium, with an onset time of 2–2.5 min and 45–65 min of predicted action. It is three times more potent than atracurium: this allows the administration of smaller doses, with fewer adverse effects. The main metabolic pathway is represented by Hofmann elimination, leading to the production of laudanosine. Less histamine is released, with lower incidence of cardiovascular adverse effects. Critically ill patients with severe sepsis may have a delayed and reduced response to standard dosing regimens.

Mivacurium has an onset of action comparable to that of atracurium (2.2–3 min) but is a short-acting compound (16–23 min) because of rapid hydrolysis by plasmatic cholinesterase. The duration of action could increase in those patients with hepatic or renal insufficiency and consequently depressed plasmatic cholinesterase activity. Small doses (0.15 mg/Kg) do not lead to major cardiovascular adverse effects; however, hypotension could occur in the case of larger doses, because of histamine release. Little information is available about the use of mivacurium in ICU [2]. A comparison is shown in Table 9.1.

9.3 Clinical Use in ICU

9.3.1 Sedation and NMB

Regarding daily sedation interruption (DSI), a recent systematic review from Burry Lisa found no strong evidence that DSI alters the duration of mechanical ventilation, mortality, length of ICU or hospital stay, adverse event rates, drug consumption, or quality of life for critically ill adults receiving mechanical ventilation compared to sedation strategies that do not include DSI. However, those results are not conclusive given the statistical and clinical heterogeneity identified in the included trials. Further studies need to be conducted [3].

Table 9.1 Comparison between principal neuromuscular blocking agents

Drug	Dose	Onset/acting	Metabolism	Adverse effects	Warning
Succinylcholine	B: 1–1.5 mg/Kg C.I.: 36–57 mcg/Kg/min	30–60 s/2–10 min	Plasmatic acetylcholinesterase	Muscle pain, tachycardia, bradycardia, ventricular arrhythmias, hypertension, increase in intraocular pressure, hyperkalemia, malignant hyperthermia	CKD, burn patients, penetrating eye injuries, pre-existing hyperkalemia
Pancuronium	B: 0.05–0.1 mg/Kg A.D.: 0.01–0.02 mg/Kg	150–220 s/75 min	Renal excretion biliary excretion liver (3-hydroxypancuronium)	Hypertension, tachycardia and increased cardiac output due to vagal blockade, reduced intraocular pressure	Increased acting: hypokalemia, hypocalcemia, myasthenia gravis, CKD
Vecuronium	B: 0.08–0.1 mg/Kg A.D: 0.02–0.03 mg/Kg C.I.: 0.8–1.2 mcg/Kg/min	120–180 s/30–35 min	Liver (active compound) Renal excretion	Histamine release, skeletal muscle weakness	Possible cross-sensitivity if previous anaphylaxis with NMBAs. Increased acting: CKD, hepatobiliary obstruction
Rocuronium	B: 0.6–1 mg/Kg A.D.: 0.075–0.15 mg/Kg C.I.: 7–12 mcg/Kg/min	60–90 s/30–40 min	Renal excretion Biliary excretion	Hypotension, tachycardia, histamine release	Possible cross-sensitivity if previous anaphylaxis with NMBAs. Increased acting: CKD, hepatobiliary obstruction, MODS
Atracurium	B: 0.3 e 0.6 mg/Kg A.D.: 0.1–0.2 mg/Kg C.I.: 4.5–13 mcg/Kg/min	90–120 s/35–43 min	Hofmann degradation A specific esterases Renal excretion	Hypotension, histamine release, sympathetic ganglionic blockade	Possible cross-sensitivity with cisatracurium. Increased acting: acidosis and severe hypothermia
Cisatracurium	B: 0.15 mg/Kg (propofol) 0.1–0.4 mg/Kg (opioids) A.D.: 0.03 mg/Kg C.I.: 1–3 mcg/Kg/min	120–150 s/45–65 min	Hofmann degradation	Hypotension, bradycardia, histamine release (laudanosine)	Possible cross-sensitivity with atracurium. Increased acting: acidosis and severe hypothermia, isoflurane, halothane, ketamine
Mivacurium	B: 0.25 mg/Kg (0.15 mg/Kg + 0.10 mg/Kg after 30 s) A.D.: 0.1 mg/Kg C.I.: 8–10 mcg/Kg/min	130–170 s/16–23 min	Plasmatic cholinesterase	Histamine release, hypotension, tachycardia, rash, bronchospasm	Increased acting: liver dysfunction, halothane

B bolus, *C.I.* continuous infusion, *A.D.* additional dose, *NMBAs* neuromuscular blocking agents, *CKD* chronic kidney disease, *MODS* multiple organ dysfunction syndrome

NMBAs do not have sedative, amnestic, or analgesic properties, so an adequate sedation and analgesia is mandatory before starting the administration of NMBAs. Based on the Richmond Agitation-Sedation Score (RASS), the ideal level of sedation is −2 (light sedation). Non-benzodiazepine sedatives should also be preferred [4].

Furthermore, NMBAs do not prevent muscles from contracting after direct stimulation. Their use in ICU could be useful to enhance mechanical ventilation, improve oxygenation and gas exchange, and diminish the risk of ventilator-associated lung injury. Sedation is useful but not sufficient, especially in nonconventional ventilator strategies such as prone positioning, permissive hypercapnia, high frequency oscillatory ventilation, and the use of high levels of PEEP. In addition to this, transpulmonary pressures are reduced, potentially minimizing the risk of overstretch on alveoli. Other therapeutic uses include preventing movement in patients with increased intracranial pressure, resolution of tetanus, and rapid sequence intubation in emergency situations [5].

9.3.2 Mechanical Ventilation and ARDS

Partial neuromuscular blockade facilitates lung-protective ventilation during partial ventilatory support while maintaining diaphragm activity in sedated patients with lung injury [6].

A meta-analysis by Alhazzani et al. found that a 48-h continuous infusion of cisatracurium reduced the risk of death at 28 days, ICU discharge, and hospital discharge. In addition, there is a decreased risk of barotrauma, and no effects are detected in the duration of mechanical ventilation or in the risk of ICU-acquired weakness. The study found that in every nine patients affected by ARDS receiving continuous infusion of cisatracurium, one life is saved during the first 90 days of hospital stay. This magnitude of effect is larger than that achieved with low-tidal-volume ventilation. Furthermore, ventilator-free days were increased in the cisatracurium group, as a result of competing risks of death and duration of ventilation, both of which are integrated into this outcome [7].

9.3.3 Sepsis

In a study by Steingrub et al., it has been noted that in septic patients who have undergone mechanical ventilation, early prescription of NMBAs during the hospital course is associated with lower mortality in comparison to those that have not received NMBAs as well as those with retarded treatment. Estimated reduction in mortality associated with receipt of neuromuscular blocking agent therapy was 4.3% (95% CI -11.5, 1.5%) [8]. The Surviving Sepsis Campaign recommends the use of NMBAs <48 h in adult patients with ARDS, as does Murray et al. There are no indications concerning curarization in septic patients, excluding those presenting ARDS [9]. It is important to mention that patients with septic shock, presenting acidosis and multiple organ dysfunction syndrome, tend to have a delayed metabolism for NMBAs.

9.3.4 General Considerations

Among the various serious adverse reactions to these drugs, secondary infection and ICU-acquired weakness may place a burden on the health-care system by resulting in substantial cost and long-term morbidity. Modern ICU practices favor lower doses of corticosteroids and a very short course of short-acting curare for the management of sepsis or ARDS. Recent trials provided no evidence for increased risk of secondary infections or critical illness neuromyopathy in patients with sepsis or ARDS with the use of corticosteroids or neuromuscular blockers [10].

9.3.5 Discontinuation and Reversal

Discontinuation of neuromuscular blockade must be a gentle process, during which analgesia and sedation adequate for patient comfort must be maintained. Partial reversal of the action of non-depolarizing NMBAs could be obtained with administration of an anticholinesterase drug (classically neostigmine 0.025–0.05 mg/Kg depending on TOF ratio or number of twitches). For neostigmine, doses exceeding 0.07 mg/Kg are unlikely to achieve any additional effect, because no further increase of ACh could be achieved. Side effects of ACh can be prevented with the coadministration of atropine (0.015 mg/Kg) or glycopyrronium bromide (7 mcg/Kg) [11].

Rocuronium and vecuronium, with their steroidal core, can be reversed by administration of sugammadex. Sugammadex is a γ-cyclodextrin with negative charged extension that binds quaternary ammonium of the target NMBA, and it is the first drug of a new class of medications called selective relaxant binding agents (SRBA). The complex resulting from the binding of the two drugs is excreted by the kidney, without any metabolic modification. Sugammadex indicates reversal of NMBAs effects in the perioperative setting; its use in the ICU setting is not well defined so far. Regarding safety issues, the major concerns are bradycardia and allergic reaction. Recommended posology varies from 2–4 mg/Kg (with 1–2 post-tetanic count) to 16 mg/Kg in case of emergency rescue (achievement of a 0.9 TOF ratio in around 90 s) [12].

9.4 Intensive Care Unit Settings

Generally, critically ill patients present organ dysfunction, so benzylisoquinolines may be preferable in ICU patients as they are not affected by renal or hepatic disease. However, Hoffman degradation could be affected by pH and temperature alterations.

Another factor to take into account is the amount of drugs given to ICU patients: several interactions with NMBAs can occur; some of these are shown in Table 9.2 [2].

Table 9.2 Drug interactions with neuromuscular blocking agents

Effect	Drug	Notes
Enhanced effect of NMBAs	Magnesium	Reduces ACh release
	Potassium	Reduces ACh release/K^+-Ca^{++} flux
	Lithium	Reduces ACh release
	Ca^{++}-blockers	Reduces neurotransmitter release
	Procainamide	Blocks nicotinic receptor
	Quinidine	Blocks nicotinic receptor
	Inhalational anesthetic	Postsynaptic receptor blockade
	Corticosteroids	Pre- and postjunctional effect (hypothesis)
	Cyclosporine	Inhibit NMBAs metabolism
	Cyclophosphamide	Reduces plasmatic cholinesterase
	Aminoglycoside	Reduces ACh release[a]
	Tetracycline	Reduces ACh release[a]
	Clindamycin	Interferes with muscle contraction
	Vancomycin	
	Furosemide	Increase intracellular-extracellular potassium ratio
Reduced effect of NMBAs	Calcium	Increases ACh release
	Phenytoin	Reduces ACh release/increases ACh sensitivity
	Ranitidine	Increases ACh release/anticholinesterase activity
	B-blocker	Especially seen with atenolol and propranolol
	Furosemide	Increase renal excretion

NMBAs neuromuscular blocking agents, *ACh* acetylcholine
[a]Not reversible with neostigmine

9.4.1 Cardiac ICU and ECMO

In the cardiac ICU setting, many different types of patients are treated, from post-cardiac surgery to post-cardiac arrest. Another feature of this type of ICU is the use of advanced support devices such as intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), etc.

Most of the studies regarding adjuvants to mechanical ventilation are focused predominantly on patients with ARDS; however, observational data suggest that similar interventions are used in patients with acute respiratory failure (ARF) even if the formal ARDS criteria are not met. ECMO, inhaled pulmonary vasodilators, and continuous NMBAs are used despite inconclusive evidence of benefit or possible harm. In recent years, an increase in the use of ECMO, and no change in the use of continuous infusion of NMBAs, was observed.

For NMBAs, the absence of adoption could be attributed to the uncertainty surrounding benefit, the absence of instant patient improvement (increase in oxygenation), or concerns about harm. Although the continuous NMBA trial did not demonstrate an increased risk of critical care polyneuropathy, anecdotal experience or concern about this risk might be driving lack of adoption until further confirmatory evidence shows consistent results. Knowledge of ongoing trials may also

suggest equipoise, which may also be a factor in the lack of adoption seen for continuous NMBAs [13].

In the specific cohort of ECMO patients, the majority receive prolonged infusion of NMBAs, up to 35% for >24 h. However, the infusion of NMBAs requires an increased use of sedatives, for which reason the trend is to reduce the use of these adjuvants [14, 15].

The population seeming to benefit most from the infusion of NMBAs is that of post-cardiac arrest patients. In out of hospital cardiac arrest (OCHA), early NMB that is sustained for a 24-h period is associated with an increased probability of survival; furthermore, the use of NMBAs seems to favor lactate clearance [16].

9.4.2 Postanesthesia Care Unit (PACU)

An increased risk of critical respiratory events and a significant prolongation of the stay in the postanesthesia care unit (PACU) are associated with residual NMB. As a result, a TOF ratio ≥0.9 has been suggested as the minimally acceptable level of recovery of neuromuscular function. This ratio has been proposed because even mild residual paralysis (TOF ratio 0.7–0.9) is associated with pharyngeal and esophageal dysfunction, obstruction of the upper airway, impaired hypoxic ventilatory response, and patient discomfort. Although most patients with residual NMB do not present critical respiratory events, some patients can develop pneumonia or atelectasis, sometimes requiring noninvasive mechanical ventilation (NIMV) or even reintubation [17].

9.4.3 Neurological/Neurosurgical ICU

Although in theory NMB can prevent movements that increase intracranial pressure (ICP) as shivering, cough, and suctioning, at the moment, the use of NMBAs in this setting is not well supported. In addition to the potential side effects, curarization could hide posttraumatic seizure activity. The only potential advantage of NMBAs seems to be the ventilation management of traumatic brain injury (TBI) patients. In fact the avoidance of asynchrony with the ventilator could decrease the risk of volotrauma and barotrauma and improves ICP control reducing intrathoracic pressure [18]. The use of NMBAs can also result in subluxation of unstable spinal fractures.

9.5 ICU Monitoring and NMB

9.5.1 Neuromuscular Monitoring

NMB may be monitored with a supramaximal stimulation (above 25% of maximal stimulus) of a peripheral nerve and measuring the muscular response to this stimulation. Patterns of stimulation include:

Single twitch: a stimulus is applied for a period of about 0.2 ms, at regular intervals. The major limitation to this technique is the need to measure a control twitch before administering the neuromuscular blocking agent.

Train of four: in this pattern, stimulation is applied with a frequency of 2 Hz, four stimuli in total. The train of stimuli is then repeated every 10 s. With this kind of monitoring, it is possible to compare the first twitch of TOF with the fourth one (TOF ratio). Monitoring of TOF ratio is important, because a ratio of 0.9 should be achieved before tracheal extubation. With non-depolarizing agents, TOF shows a decrease from the first twitch to the fourth (TOF fade). On the other hand, succinylcholine provokes an equal decrease in all the twitches; with phase II block, TOF fade is observed.

Tetanic stimulation: consists in a high-frequency (50–200 Hz) stimulation for a limited amount of time. This pattern of stimulation is very sensitive and can elicit minor degrees of neuromuscular block, which is potentially useful in the postoperative recovery room. However, its use is limited by the fact that tetanic stimulation is extremely painful.

Double burst stimulation: two short stimuli of 50 Hz are given; partially paralyzed with a non-depolarizing agent, the response to the second burst is reduced. The ratio of the magnitude of the second stimulus to the first is known as the DBS ratio.

Post-tetanic count: this stimulation could be useful in deep NMB block, because tetanic stimulation could elicit a response after the stimulation [19] (Table 9.3).

A major finding from a study by Bouju et al. was that the objective of TOF count of 1 or 2 was obtained in only less than 10% of the measurements when patients are monitored only according to clinical assessment, even though the NMBA infusion rates were in accordance with the recommendations [20].

Rudis et al. compared patients paralyzed with an aminosteroid managed with a clinical assessment with those managed with a TOF for an objective of 1/4. A faster recovery of muscle paralysis and return to spontaneous ventilation, with a decrease in the amount of infused NMBAs, was observed in the TOF group [21].

9.5.2 Bispectral Index (BIS)

In BIS monitoring an electrode is applied on the patient's forehead, recording electrical activity from the cerebral cortex. The signal is then converted to a quantitative

Table 9.3 Different neuromuscular stimuli

Type	Frequency	Duration	Interval	Repetition	Application
Single twitch	0,1 Hz	0,2 ms	1–10 s	10–1 s	Anesthesia induction
Tetanus	50 Hz	5 s		>6 min	
TOF	2 Hz	2 s	10 s	10 s	Induction, maintenance, intubation, awakening, ICU
PTC	50 Hz	2 s		>6 min	Deep block
DBS	50 Hz	40 ms	750 ms	>6 min	Residual curarization

index varying from 100 (awake) to 0 (flatline). Values of 70, 60, 40, and 20 correspond, respectively, to deep sedation, general anesthesia, deep hypnotic state, and burst suppression [22].

The typical setting of BIS monitoring is OR, but the use of prolonged sedation and NMBAs moves the field of action also into ICU. BIS may be useful to prevent both awareness and oversedation. However, BIS is not always reliable and must be tailored to the single patient. Currently, clinical decisions made on the basis of BIS monitoring in ICU should be limited to preventing over- or under-sedation in the appropriate clinical settings and to providing feedback on induced burst suppression when continuous EEG is not available [23].

In a retrospective observational study, Tasaka et al. observed that one out of ten critically ill patients receiving therapeutic paralysis may be inadequately sedated. In this study, BIS provided high sensitivity for unarousable to light levels of sedation, but data were insufficient to make solid conclusions about the ability of BIS to detect inadequate sedation [24].

Regarding interaction of drugs with BIS monitoring, curarization by rocuronium during light propofol-remifentanil anesthesia results in a decrease in BIS values, and a subsequent antagonization of NMB by sugammadex during surgical anesthesia does not result in a change in BIS values [25].

9.6 Guidelines

The 2016 update on NMBA management in the critically ill patient contains the following recommendations:

Early administration of continuous NMBAs in the course of acute respiratory distress syndrome for patients with a PaO_2/FiO_2 ratio less than 150.

Routine administration of NMBAs to mechanically ventilated patients with status asthmaticus should be avoided.

A trial of an NMBA in life-threatening situations associated with profound hypoxemia, respiratory acidosis, or hemodynamic compromise is suggested.

NMBAs may be used to manage overt shivering in therapeutic hypothermia.

TOF monitoring could be useful for monitoring NMB but only if incorporated in an inclusive assessment of the patient, comprehensive of clinical assessment.

Peripheral nerve stimulation with TOF alone should be avoided as monitoring in patients receiving continuous infusion of NMBAs.

Structured physiotherapy is recommended in patients receiving continuous infusion of NMBAs.

A blood glucose level of <180 mg/dL should be the target in all patients receiving continuous infusion of NMBAs.

For obese patients, consistent weight (e.g., ideal body weight) should be used to calculate NMBA doses.

NMBAs should be discontinued at end-of-life or when life support is withdrawn [26].

9.7 Adverse Effects

9.7.1 Infections

Hospital-acquired infection is a major concern for patients, health-care staff, and policy makers. Some interventions, such as NMBA infusion, are related to an increased risk of infection in ICU patients. NMBAs may inhibit movement of the bronchial ciliary apparatus, with consequent accumulation of secretions. In addition to this, there is an increasing risk of aspiration of oropharyngeal bacterial flora due to the dysfunction of the swallowing reflex. NMB is suggested as an independent risk factor for ventilator-associated pneumonia, both in general ICU patients, in those with traumatic brain injury, and in post-cardiac arrest care. However, a recent trial conducted by Papazian et al. did not report an increased risk of ventilator-associated pneumonia with the use of cisatracurium in patients with ARDS [10, 27].

9.7.2 Deep Venous Thrombosis (DVT)

Recalling the triad of Virchow (hemodynamic changes, endothelial injury, hypercoagulability), it is clear that the critically ill patient with infusion of NMBAs is subject to blood stasis. In addition to this, many ICU patients have at least one of the other risk factors for thrombosis. A recent study of Boddi et al. reported that the use of NMBAs is the strongest predictor for the development of ICU-related DVTs. The same trial reported that educational initiatives to promote DVT prophylaxis (both mechanical and pharmacologic) significantly reduced the prevalence of DVTs. Closer neuromuscular monitoring coupled with protocols to guide titration of NMBAs may also contribute to reducing the DVT prevalence [28].

9.7.3 Corneal Abrasion

Abolition of the blink reflex and paralysis of eyelids can result in drying, scarring, ulceration, and subsequent infection of the eye. From 8 to 60% of the patients admitted to ICU present corneal abrasions. A possible strategy to reduce the prevalence of ophthalmic complication could be the use of eye protection prophylaxis (tear replacement, artificial ointments, eye covers, etc.).

9.7.4 Anaphylaxis

Patients may develop anaphylaxis after the first dose of NMBA due to cross-reactivity with other inciting agent exposures. The allergenic component seems to be the ammonium. Seven consecutive large French surveys over an 18-year period suggested that NMBAs are the most frequent perioperative agents (more than sedatives, hypnotics, latex, antibiotics, and colloids) involved in allergic reactions [2].

Table 9.4 Comparison between cardiovascular side effects of NMBAs

Drug	Heart rate	Blood pressure	Cardiac output
Succinylcholine	+	+	+
Pancuronium	+	+	+
Vecuronium	–	=/– (**rare**)	–
Rocuronium	+/–	=/–	=/–
Atracurium	–	–	–
Cisatracurium	=/–	=/–	=/–
Mivacurium	+	–	=/–

9.7.5 Cardiovascular Effects

Many adverse cardiovascular side effects are reported with the use of NMBAs. The two main mechanisms of those effects are vasodilation after histamine release and sympathetic ganglionic blockade.

While succynilcholine and pancuronium have a predominantly positive effect that may help in counteracting side effects of sedation agents, atracurium and mivacurium are prone to cause a decrease in blood pressure values.

A comparison is shown in Table 9.4.

9.7.6 Prolonged Paralysis and ICU-Acquired Weakness

Prolonged paralysis following drug discontinuation results from accumulation of drug or active metabolites or an acute myopathy. It is a rare disorder related to prolonged use (days) of paralytic agents, often in the setting of renal or hepatic insufficiency. Affected patients have flaccid areflexic tetraplegia.

A modest association between the use of neuromuscular blocking drugs and neuromuscular dysfunction acquired in critical illness, including ICU-acquired weakness (ICU-AW), critical illness polyneuropathy (CIP), and critical illness myopathy (CIM), has been reported. The risk of critical illness polyneuropathy was greater in patients with severe sepsis or septic shock or more severe illness [29].

Proposed mechanisms for ICU-AW include disturbances in the microcirculation, protein malnutrition, systemic inflammation, and prolonged immobility. To date there are not enough solid studies that demonstrate correlation with NMBA use. Two recent trials did not identify an increased prevalence of ICU-AW in ARDS patients administered with a 48-h cisatracurium infusion. Future investigations should examine the impact of other factors, such as corticosteroids, sedation use, type, and duration of NMBAs [2].

9.7.7 Critical Illness Neuropathy and Myopathy

CIP and CIM have an important impact on the outcome of patients in the ICU. They typically cause muscle weakness and paralysis and impair rehabilitation in up to

100% of patients staying in the ICU for at least 4 weeks. CIP/CIM itself may prolong the need for ventilatory support as the phrenic nerve and diaphragmatic muscle can be involved. CIP/CIM is associated with increased ICU and hospital stays and elevated mortality rates [30, 31]. The pathophysiology of CIP/CIM is complex and still unclear. It is hypothesized that increased capillary permeability allows NMBAs to cross the membrane and have direct toxic effects on the nerve or cause functional denervation of muscle.

Most authors agree on aggressive treatment of sepsis as the most important measure to reduce the incidence of CIP/CIM. NMBAs, if indicated, should be used at a minimal dose for as short a period as possible [32].

CIM and CIP together fall under the classification of critical illness myopathy and/or neuropathy (CRIMYNE). A recent Italian multicenter study found that a criterion to identify patients with CRIMYNE is a peroneal compound muscle action potential (CMAP) reduction below two standard deviations of normal value [33]. This meta-analysis by Price et al. suggests a modest association between neuromuscular blocking agents and neuromuscular dysfunction acquired in critical illness; limitations include studies with a high risk of bias [34].

It is important to distinguish between prolonged neuromuscular block from drug overdosage or the effect of drug metabolites and CRIMYNE.

9.7.8 Overdosage

Overdosage, as well as the long-term use of NMBAs, can result in the accumulation of drugs or metabolites with intrinsic activity. The drug is stored in the basement membrane of the neuromuscular junction, which then acts as a reservoir; in addition to this, drug clearance decreases. Overdose is not only due to errors in the drug preparation but also to the failure of titration in the case of electrolyte imbalance or acid-based disturbances [35].

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