Anesthetic Management Of Patients With Myopathies

Essay

Submitted for partial fulfillment of master degree in anesthesiology

By

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M.B.B.CH

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المعالجة التخديرية للمرضى المصابين بالإعتلال العضلي

توطئة للحصول على درجة الماجستير في التخدير

مقدمة من

الطبيب /غادة احمد سعد الدين

بكالوريوس الطب والجراحة

كلية الطب

جامعة بنها

تحت اشراف

الاستاذ الدكتور/ ايهاب الشحات عفيفي

استاذ التخدير والعناية المركزة

كلية الطب – جامعة بنها

الدكتور/ محمد فؤاد المليجي

مدرس التخدير والعناية المركزة

كلية الطب – جامعة بنها

كلية الطب

جامعة بنها

2019

بسم الله الرحمن الرحيم

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

البقرة آية (32)

Acknowledgment

First and foremost, thanks to **(ALLAH),** the Most Gracious and the Most Merciful, who granted me to finish this work.

Prayer and peace be upon the most honorable of Messengers **(MOHAMAD).**

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Ghada Ahmed Saad Eldin

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LIST OF ABBREVIATIONS

Ach	Acetyl choline
EPPs	End plate potentials
ED 95	Effective Dose
TOF	Train of four
NMJ	Neuro muscular junction
NMBAs	Neuro muscular blocking agents
ACHE	Anti choline estrase
ECG	Electro cardio graphy
S	Seconds
ml	millilitre
Kg	kilogram
ms	millisecond
Hz	Hertz
NDNMB	Non depolarizing neuro muscular blocking
NEOST	Neostigmine
PTC	Post tetanic count
PORC	Post operative residual curarization
PT	Physical therapy
DBS	Double burst stimulation
MMG	Mechanomyography
EMG	Electromyography
HIV	Human immunodeficiency virus
NMDs	Neuro muscular disorders
BIS	Bi-spectral index monitor
MH	Malignant hyperthermia
CK	Creatine kinase

CCD	Central core disease
FVC	Forced vital capacity
MEP	Maximum expiratory pressure
PCF	Peak cough flow
SPO2	Peripheral capillary oxygen saturation
PCO2	Partial pressure of carbon diaoxide
MI-E	Mechanical insuflator-exsufflator
NIV	Non invasive ventillation
DMD	Duchenne muscular dystrophy
I.V	Intravenous
K+	Potassium
GA	General anaethesia
TCI	Target controlled infusion
GSD	Glycogen storage disease
RYR1	Ryanoide Receptor 1
PH	Potential hydrogen
meq	milliequvilant
L	Litre
ACLS	Advanced cardiac life support
ICU	Intensive care unit

INTODUCTION

A myopathy is a muscle disease unrelated to any disorder of innervation or neuromuscular junction. These conditions have widely varying etiologies, including congenital or inherited, idiopathic, infectious, metabolic, inflammatory, endocrine, and drug-induced or toxic (**Muntean DM;et al.,2017**)

patients with neuromuscular disorders may have altered vital function(weakness of respiratory muscle,scoliosis,cardiac involvment) which increase the risk of surgical procedures requiring general anesthesia or sedation (**Birnkrant DJ,2009**).

patients with some NMDs anesthetic agents can trigger life-threatening reactions namely malignant hyperthermia(MH),rhabdomyolysis or hyperkalaemic cardiac arrest secondary to denervation (**Wappler F;2010**)

The anaesthetic management of patients with myopathies is challenging, The pre-anaesthetic assessment aims at the detection of potentially undiagnosed myopathic patients and in case of known or suspected muscular disease on the quantification of disease progression(**Gray RM;2017**).

Detailed diagnosis is essential to asses the risk during surgery or anesthesia thus, preoperative assessment must include neurological examination to confirm the diagnosis and level of progression of the disease (**Ciafaloni E,Fox DJ,et al.,2009**).

Assessment of respiratory function should include an accurate medical history and physical examination, a chest x-ray ,an evaluation of sleep- disordered breathing and the measurement of respiratory function

and cough effectiveness **(Vianello A, Arcaro G,et al.,2011)**.

Patient with NMDs should undergo a careful assessment of heart function as well as optimization of cardiac therapies before anethesia or sedation, an electrocardiogram and echocardiogram should be performed before anethesia or sedation if not done in the previous 12 months **(Richa FC,2011).**

Intra operative managment of patients with myopathies aims at avoiding GA and preferring regional anethesia whenever possible,if GA is unavoidable ultra shorting drugs as propofol and remifentanil are preferable ,succinylcholine must be avoided,volatile anethetics is usually considered at high risk for life threatening complications.**(Blichfeldt-Lauridsen L,et al.,2012)**

post operative managment of patients with myopathies aims at adequate pain control to prevent hypoventilation after thoracic,upper abdominal and spine surgeries and requring close monitoring and agressive respiratory management **(Von Breunig F,Goetz AE,et al.,2012)**

Patients with myopathies are at high risk of intraoperative and postoperative complications so, an intensive proactive, multidisciplinary approach should be instituted before,during and after any surgical procedure requiring GA or sedation in a fully equppied hospital with extensive experience in their managment **(Muenster T, Mueller C,et al.,2012).**

Aim of the Work

The aim of our study is to discuss the proper managment of patient with myopathy to avoid the possible complications of anesthesia on these patients as, malignant hyperthermia, acute rhabdomyolysis, metabolic acidosis ,hyperkalaemia and cardiac arrhysmia.

Chapter 1

Anatomy and physiology of the muscles

Anatomy of the muscles

Types

There are three types of muscle tissue recognized in vertebrates:

- Skeletal muscle or "voluntary muscle" is anchored by tendons to bone and is used to effect skeletal movement ,these muscles are responsible to react to conscious control,

- Smooth muscle or "involuntary muscle" is found within the walls of organs such as the esophagus, stomach, intestines, bronchi and uterus. Unlike skeletal muscle, smooth muscle is not under conscious control.

- Cardiac muscle (myocardium), is also an "involuntary muscle" and is found only in the heart, (**Alfred Carey Carpenter, 2007**)
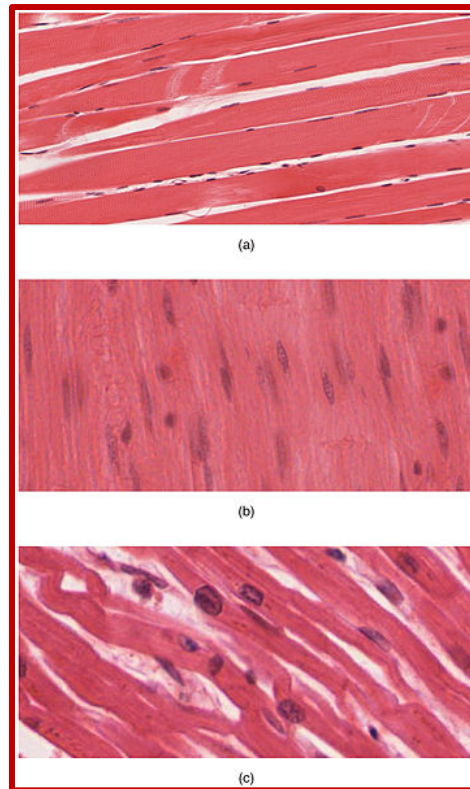
Figure 1 types of muscle tissue, (Alfred Carey Carpenter, 2007)

(a) skeletal muscle, (b) smooth muscle, and (c) cardiac muscle.

Structure

The anatomy of muscles includes gross anatomy, which comprises all the muscles Structure of an organism, and microanatomy, which comprises the structures of a single muscle.

Microanatomy

the overall muscle consists of fibers (cells) that are bundled into fascicles, which are themselves grouped together to form muscles. At each level of bundling, a collagenous membrane surrounds the bundle, Scattered throughout the muscles are muscle spindles that provide sensory feedback information to the central nervous system. Within the cells of the muscle are myofibrils, which themselves are bundles of protein filaments. organized together into repeating units called

sarcomeres. The filaments in a sarcomere are composed of actin and myosin**, (Kent, et al 1987).**

Gross anatomy

The tough, fibrous epimysium of skeletal muscle is both connected to and continuous with the tendons. In turn, the tendons connect to the periosteum layer surrounding the bones, permitting the transfer of force from the muscles to the skeleton, **(MacIntosh, et al 2006.)**

Development

All muscles are derived from paraxial mesoderm. The paraxial mesoderm is divided along the embryo's length into somites, corresponding to the segmentation of the body, Each somite has 3 divisions, sclerotome (which forms vertebrae), dermatome (which forms skin), and myotome (which forms muscle). The myotome is divided into two sections, the epimere and hypomere, which form epaxial and hypaxial muscles, respectively. **(Sweeney, et al 1997)**

<u>Physiology of the muscles</u>

Contraction

The three types of muscle have significant differences. However, all three use the movement of actin against myosin to create contraction. In skeletal muscle, contraction is stimulated by electrical impulses transmitted by the nerves, Cardiac and smooth muscle contractions are stimulated by internal pacemaker cells All skeletal muscle and many smooth muscle contractions are facilitated by the neurotransmitter acetylcholine. Each skeletal muscle contains long units called myofibrils, and each myofibril is a chain of sarcomeres. Since contraction occurs at

the same time for all connected sarcomeres in a muscles cell, these chains of sarcomeres shorten together, thus shortening the muscle fiber, resulting in overall length change. **(Kardong, et al 2015)**

Nervous control
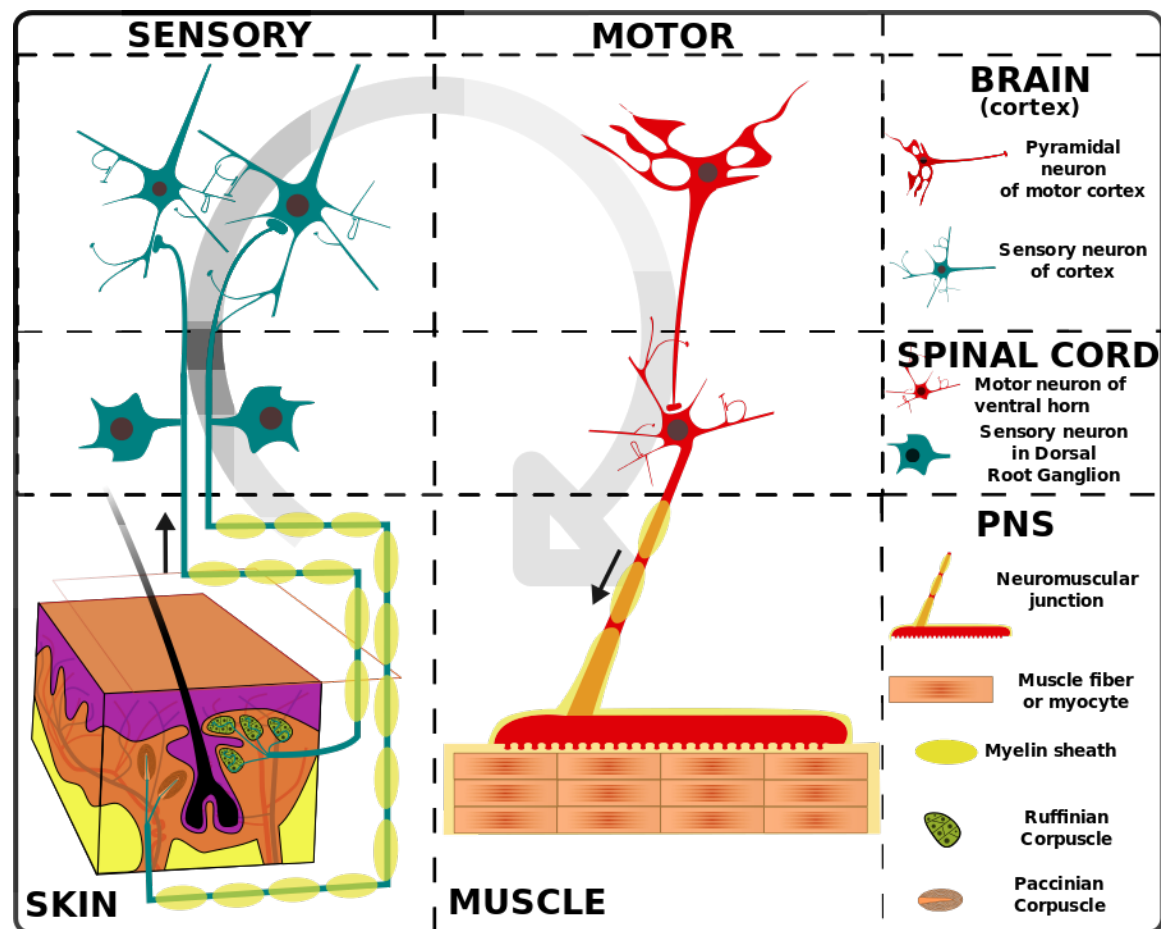
Figure 2 Simplified schema of basic nervous system function.

Signals are picked up by sensory receptors and sent to the spinal cord and brain via the afferent leg of the peripheral nervous system, whereupon processing occurs that results in signals sent back to the spinal cord and then out to motor neurons via the efferent leg. **(Larsson, L, et al 1991)**

Physiological strength

Muscle is a result of three factors that overlap: physiological strength (muscle size, cross sectional area, available crossbridging, responses to training), neurological strength (how strong or weak is the signal that tells the muscle to contract), and mechanical strength (muscle's force angle on the lever, moment arm length, joint capabilities). **(McGinnis, et al 2013)**.

Table 1 Grading of muscle strength (McGinnis, et al 2013)

Grade 0	No contraction
Grade 1	Trace of contraction, but no movement at the joint
Grade 2	Movement at the joint with gravity eliminated
Grade 3	Movement against gravity, but not against added resistance
Grade 4	Movement against external resistance, but less than normal
Grade 5	Normal strength

Chapter 2

Pharmacology of muscle relaxants

Classification

These drugs fall into two groups:

- **Non-depolarizing blocking agents:** These agents constitute the majority of the clinically relevant neuromuscular blockers. They act by competitively blocking the binding of ACh to its receptors, and in some cases, they also directly block the ionotropic activity of the ACh receptors.

- **Depolarizing blocking agents:** These agents act by depolarizing the sarcolemma of the skeletal muscle fiber. This persistent depolarization makes the muscle fiber resistant to further stimulation by ACh. **(W. C. Bowman ,2006)**.

Non-depolarizing blocking agents

A neuromuscular non-depolarizing agent is a form of neuromuscular blocker that does not depolarize the motor end plate. The quaternary ammonium muscle relaxants belong to this class. **(Bufler J, et al 1996).**

Below are some more common agents that act as competitive antagonists against acetylcholine at the site of postsynaptic acetylcholine receptors. Tubocurarine, found in curare of the South American plant Pareira, Chondrodendron tomentosum, is the prototypical nondepolarizing neuromuscular blocker. It has a slow onset (>5 min) and a long duration of action (30 mins). Side-effects include hypotension,

which is partially explained by its effect of increasing histamine release, a vasodilator, as well as its effect of blocking autonomic ganglia. It is excreted in the urine. **(Inada E, et al 1986)**

This drug needs to block about 70–80% of the ACh receptors for neuromuscular conduction to fail, and hence for effective blockade to occur. At this stage, end-plate potentials (EPPs) can still be detected, but are too small to reach the threshold potential needed for activation of muscle fiber contraction.**(Ostergaard D, et al 1989)**

Table 1: Comparison of non-depolarizing neuromuscular blocking agents (Rang, H. P,2003)

Agent	Time to onset (seconds)	Duration (minutes)	Side effects	Clinical use	Storage
Rapacuronium (Raplon)					
Mivacurium (Mivacron)	90	12–18	hypotension (transiently), by release of histamine[9]	No longer manufactured secondary to marketing, manufacturing, and financial concerns	refrigerated
Atracurium (Tracrium)	90	30 min or less	hypotension, transiently, by release of histamine Toxic metabolite called laudanosine, greater accumulation in individuals with renal failure	widely	refrigerated
Doxacurium (Nuromax)		long	hypotension, transiently, by release of histamine Harmful metabolite called laudanosine (lowering seizure threshold); greater accumulation in individuals with renal failure		
Cisatracurium (Nimbex	90	60–80	does not cause release of histamine		refrigerated
Vecuronium (Norcuron)	60	30–40	Few, may cause prolonged paralysis and promote muscarinic block	widely	Non-refrigerated
Rocuronium (Zemuron)	75	45–70	may promote muscarinic block		Non-refrigerated
Pancuronium (Pavulon)	90	180 or more	tachycardia (slight) (no hypotension)	widely	Non-refrigerated
Tubocurarine (Jexin)	300 or more	60–120	hypotension (by ganglion-block and histamine release) Bronchoconstriction (by histamine release)	rarely	
gallamine (Flaxedil)	300 or more	60–120	tachycardia		
Pipecuronium	90	180 or more	tachycardia (slight) (no hypotension)		Non-refrigerated

Depolarizing blocking agents

A depolarizing neuromuscular blocking agent is a form of neuromuscular blocker that depolarizes the motor end plate. An example is succinylcholine. **(Flower, et al 2007)**

There are two phases to the depolarizing block. During phase I (depolarizing phase), they cause muscular fasciculations (muscle twitches) while they are depolarizing the muscle fibers. Eventually, after

sufficient depolarization has occurred, phase II (desensitizing phase) sets in and the muscle is no longer responsive to acetylcholine released by the motoneurons. At this point, full neuromuscular block has been achieved. **(Brunton LL, et al 2006)**

The prototypical depolarizing blocking drug is succinylcholine (suxamethonium). It is the only such drug used clinically. It has a rapid onset (30 seconds) but very short duration of action (5–10 minutes) because of hydrolysis by various cholinesterases (such as butyrylcholinesterase in the blood). Succinylcholine was originally known as diacetylcholine because structurally it is composed of two acetylcholine molecules joined with a methyl group. Decamethonium is sometimes, but rarely, used in clinical practice. **(Flower, et al 2007)**

New non-depolarizing drugs

Gantacurium is a diester derivative of chlorofumaric acid belonging to the family of tetrahydroisoquinoliniums. It is undergoing phase III trials in the USA. A dose of 1.8–4 X ED_{95} (0.19 mg kg^{-1}) has a fast onset of action of 1.5 min with spontaneous recovery of the train-of-four (TOF) ratio to 0.9 in 10–14 min. It is being considered as a replacement for succinylcholine. Gantacurium is degraded non-enzymatically to inactive derivatives by the endogenous amino acid, L-cysteine, in the plasma. L-cysteine conjugates with the central double-bond carbons in gantacurium causing alkaline hydrolysis. This drug is associated with less histamine release than succinylcholine. Its neuromuscular blocking effects can rapidly be antagonized by edrophonium 0.5 mg kg^{-1} with atropine, or possibly cysteine if it becomes commercially available **(Savarese JJ, et al 2010)**

Antagonizing neuromuscular block

The action of NMBAs can be terminated either by increasing the concentration of ACh at the NMJ or by enhancing the disposition of NMBAs from the plasma. **(Srivastava A, et al 2009)**

AChE antagonists

These prevent the degradation of ACh by hydrolysing the enzyme AChE in the synaptic cleft. The enzyme has two active sites: the esteratic site (positively charged) and the anionic site (negatively charged). **(Srivastava A, et al 2009)**

Reversible inhibitors

Edrophonium competes with ACh for AChE. It has a short duration of action as it only forms an ionic not a covalent bond with AChE. It binds to the negatively charged site on the enzyme by the electrostatic attraction of its positively charged nitrogen atom.

Edrophonium is less potent than neostigmine and not commonly used in the UK. Neostigmine hydrolyses AChE by forming a carbamylated enzyme complex at the esteratic site. It has a slower rate of hydrolysis than edrophonium. The action of these antagonists is not limited to the NMJ, for they also cause cholinergic effects such as bradycardia and are given with anticholinergic agents. **(Srivastava A, et al 2009)**

Irreversible inhibitors

Organophosphorous compounds irreversibly phosphorylate the esteratic site of AChE forming a stable complex that is resistant to

hydrolysis or reactivation. They are not used in clinical practice as they cause autonomic and central nervous system instability. **(Srivastava A, et al 2009)**

Drugs which encapsulate NMBAs

Traditional pharmacological strategies only reverse residual neuromuscular block, once recovery has commenced, for example, a TOF ratio of 0.2, or a TOF count of 2. A reversal agent that could reverse profound block soon after an NMBA had been given was considered beneficial. This led to the development of sugammadex as a specific antagonist for rocuronium. **(McDonnell NJ, et al 2011)**

Sugammadex

Pharmacokinetics Sugammadex exhibits three-compartment kinetics similar to rocuronium. Protein binding, and blood–brain barrier and placental transfer are minimal. The drug and its complex are eliminated unchanged by the kidneys. Sugammadex has a volume of distribution of 10–15 litres with a plasma clearance of 91 ml min^{-1} (similar to the glomerular filtration rate), and an elimination half-life of 2.2 h. **(Srivastava A, et al 2009)**

Mechanism of action

Sugammadex encapsulates free plasma rocuronium molecules in a ratio of 1:1. As the free concentration of rocuronium in the plasma decreases, its dissociation from the NMJ increases down a concentration gradient, thus restoring normal muscle tone. Sugammadex has no effect on AChE, so co-administration of anticholinergics is not required. It is

ineffective against depolarizing NMBAs and benzylisoquinolinium compounds. **(McDonnell NJ, et al 2011)**

Dose

The dose depends on the degree of neuromuscular block. If two twitches of the TOF response are detectable (when anticholinesterases can be used), a dose of 2 mg kg^{-1} is recommended. If there is profound block (post-tetanic count of 2–4), then sugammadex 4–8 mg kg^{-1} should be given. For immediate reversal within a few minutes of giving the relaxant, the dose is 16 mg kg^{-1}. **(McDonnell NJ, et al 2011)**

Side-effects

Concern has been expressed about possible prolongation of the QT interval of the ECG after sugammadex, and hyper- and hypotension have been reported after large doses (32 mg kg^{-1}). One report described accidental administration of a very large dose of sugammadex (40 mg kg^{-1}), however, without any adverse effect on the cardiovascular system. **(McDonnell NJ, et al 2011)**

Recently, reports of anaphylaxis to sugammadex have occurred including one in a patient with a raised plasma tryptase and a positive skin PT. In contrast, it has been suggested that sugammadex could be given to mitigate the effects of rocuronium in anaphylactic shock. **(Menendez-Ozcoidi L, et al 2011)**

Postoperative residual curarization

Postoperative residual curarization (PORC) is a term used to describe residual paralysis or recurarization after anaesthesia in which

NMBAs have been used with or without AChE inhibitors. **(Debaene B, et al 2003)**

Incidence

The frequency of PORC in present-day clinical practice ranges from 4% to 50% depending on: the duration of action of the NMBA used; whether or not a reversal agent is given; the type of neuromuscular monitoring used peroperatively; and the diagnostic tests used for assessing PORC. **(Fawcett WJ, et al 1995)**

Ali and colleagues introduced a clinical tool for monitoring recovery from neuromuscular block in 1971. They suggested that if the degree of the block was assessed using the TOF twitch technique, inadequate reversal could be prevented. They recommended that a TOF ratio of 0.7 after operation indicated adequate clinical recovery from muscle relaxation as it correlated with a sustained head-lift for 5 s, ability to protrude the tongue and grip the hand, and a vital capacity of 15–20 ml kg^{-1}. Following this work, a TOF ratio of >0.7 was considered an indicator of adequate recovery before extubation for over two decades. **(Ali HH, et al 1971)**

In 1997, Berg and colleagues reported a significant incidence of postoperative pulmonary complications, if the TOF ratio was <0.7 in the recovery room. In this study, the incidence of a TOF ratio <0.7 was higher after the long-acting NMBA, pancuronium (26%), compared with those who had received the intermediate-acting relaxants, atracurium and vecuronium (5.3%). **(Berg H, et al 1997)**

At that time, Eriksson and colleagues measured the strength of the pharyngeal constrictor muscles in 14 volunteers after vecuronium-induced neuromuscular block. He concluded that pharyngeal tone only returned to normal when the TOF ratio at the adductor pollicis muscle was >0.9: a TOF ratio <0.9 increased the chance of pulmonary aspiration of stomach contents. It is now considered that a TOF ratio >0.9 is required before extubation. **(Eriksson LI, et al 1997)**

Chapter 3

Neuromuscular monitoring

In anesthesia, neuromuscular blocking agents may be required to facilitate endotracheal intubation and provide optimal surgical conditions. When neuromuscular blocking agents are administered, neuromuscular function of the patient must be monitored. **(Ortega R, et al 2018)**

Neuromuscular function monitoring is a technique that involves the electrical stimulation of a motor nerve and monitoring the response of the muscle supplied by that nerve. **(Naguib M, et al 2017)**

It may be used from the induction of to recovery from neuromuscular blockade. Importantly, it is used to confirm adequacy of recovery after the administration of neuromuscular blocking agents. **(Checketts MR, et al 2016)**

Stimulating the motor nerve

The degree of neuromuscular block can be assessed by applying a supramaximal stimulus to a peripheral nerve, and then measuring the associated muscular response. The nerve chosen to be stimulated must fulfil a number of criteria. First, it must have a motor element; second, it must be close to the skin; and third, contraction in the muscle or muscle group which the nerve supplies must be visible or accessible to evoked response monitoring. **(Ali HH, et al 1971)**

Pattern of nerve stimulation

Single twitch stimulation

A single square wave supramaximal stimulus is applied to a peripheral nerve for a period of about 0.2 ms, at regular intervals, and the evoked response is observed. The twitch response will only be depressed when a neuromuscular blocking agent occupies 75% of the post-synaptic nicotinic receptors. Twitch depression will need to be more than 90% inorder to provide good conditions for abdominal surgery. The onset of neuromuscular block can then be observed, using a single twitch at 0.1 Hz (1 twitch every 10 s). The onset and recovery from depolarizing and non-depolarizing block monitored using single twitches have a similar pattern, differing only in timescale. **(Viby-Mogensen, et al 2000)**
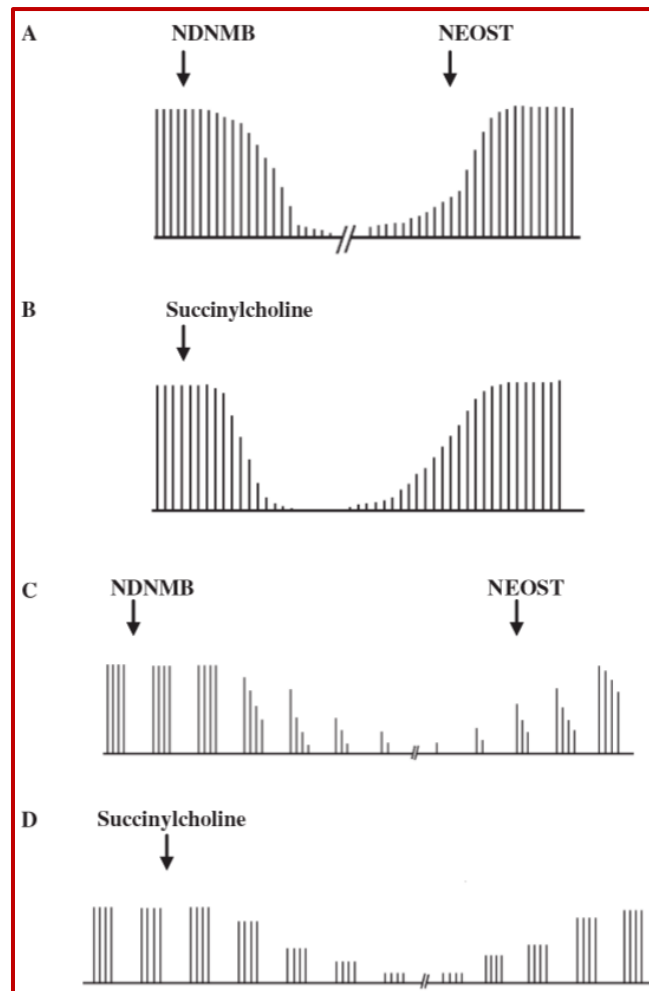
Figure 1 (A) Pattern of evoked muscle responses to twitch stimulation after administration of a non-depolarizing neuromuscular blocking drug (NDNMB), followed by antagonism with neostigmine (NEOST). NOEST hastened the rate of recovery, if the twitch has already started to increase. (B) Pattern of evoked muscle responses to twitch stimulation after administration of succinylcholine. (C) TOF monitoring of onset of neuromuscular block produced by a NDNMB, followed by antagonism with NOEST, given when three twitches of the TOF are detectable. (D) TOF monitoring of onset of, and recovery from, neuromuscular block produced by succinylcholine. (Viby-Mogensen, et al 2000)

Train-of-four stimulation

The principle was to produce a pattern of stimulation that did not require the comparison of evoked responses to a control response obtained before administration of a neuromuscular blocking drug. The pattern involved stimulating the ulnar nerve with a TOF supra maximal twitch stimuli , with afrequency of 2Hz, that is, four stimuli each separated by 0.5 s. The TOF was then repeated every 10s (train frequency of 0.1Hz). As well as enabling the observer to compare T1 (first twitch of the TOF) to T0 (control), it also enables comparison of T4 (fourth twitch of the TOF) to T1. This is known as the TOF ratio. **(Ali HH, et al 1970).**

When a non-depolarizing agent is given, a typical pattern is observed. There is a reduction in the amplitude of the evoked responses, with T4 affected first, then T3, followed by T2, and finally T1 (Fig. 3C). This decrement in twitch height is known as fade. As the non-depolarizing block becomes more intense, T4 disappears followed by T3, T2, and finally T1. The reverse is true during recovery from non-depolarizing block: T1 reappears first followed by T2, T3, and finally, T4 (Fig. 3C). **(Ali HH, et al 1970).**

During onset of non-depolarizing block, T4 disappears at about 75% depression of T1, T3 at 80–85% depression of T1, and T2 at 90% depression. During partial non-depolarizing block, the number of twitches (TOF count) correlates with the degree of neuromuscular block. Twitch suppression of 90% would equate to a TOF count of 1 or less. Reversal of residual neuromuscular block can safely be achieved when the TOF count is 3 or greater. **(Viby-Mogensen, et al 2000)**

Tetanic stimulation

Tetanic stimulation uses a high frequency (50–200 Hz) with a supramaximal stimulus for a set time: normally 5 s. In healthy skeletal muscle during normal movement, the response is maintained as a tetanic contraction. However, its use is limited by the fact that tetanic stimulation is extremely painful. **(Viby-Mogensen, et al 2000)**

Tetanic stimulation has complex effects on the neuromuscular junction especially in the presence of a neuromuscular blocking drug. Fade is thought to be an effect of a non-depolarizing agent on the presynaptic nerve membrane. During partial depolarizing block, fade is not observed in response to tetanic stimulation. The amplitude of the evoked response will be lower but the tetanic contraction will be maintained. **(Viby-Mogensen, et al 2000)**

Post-tetanic count

The main use of PTC is when profound neuromuscular block is required, for example, during retinal surgery, when movement or coughing could have devastating effects. It should be remembered that a tetanic stimulus, by mobilizing acetylcholine, might affect the neuromuscular junction of a stimulated nerve for a significant time. If two PTCs are administered in quick succession, the degree of neuromuscular block will be underestimated. It is recommended that tetanic stimulation should not be repeated for a period of 6 min. **(Viby-Mogensen, et al 2000)**

Double-burst stimulation

DBS was developed to enable the anaesthetist to detect even small degrees of neuromuscular block clinically. Significant residual neuromuscular block can be assessed using the TOF response. However, small degrees of residual block may be easier to appreciate with DBS. **(Drenck NE, et al 1989)**
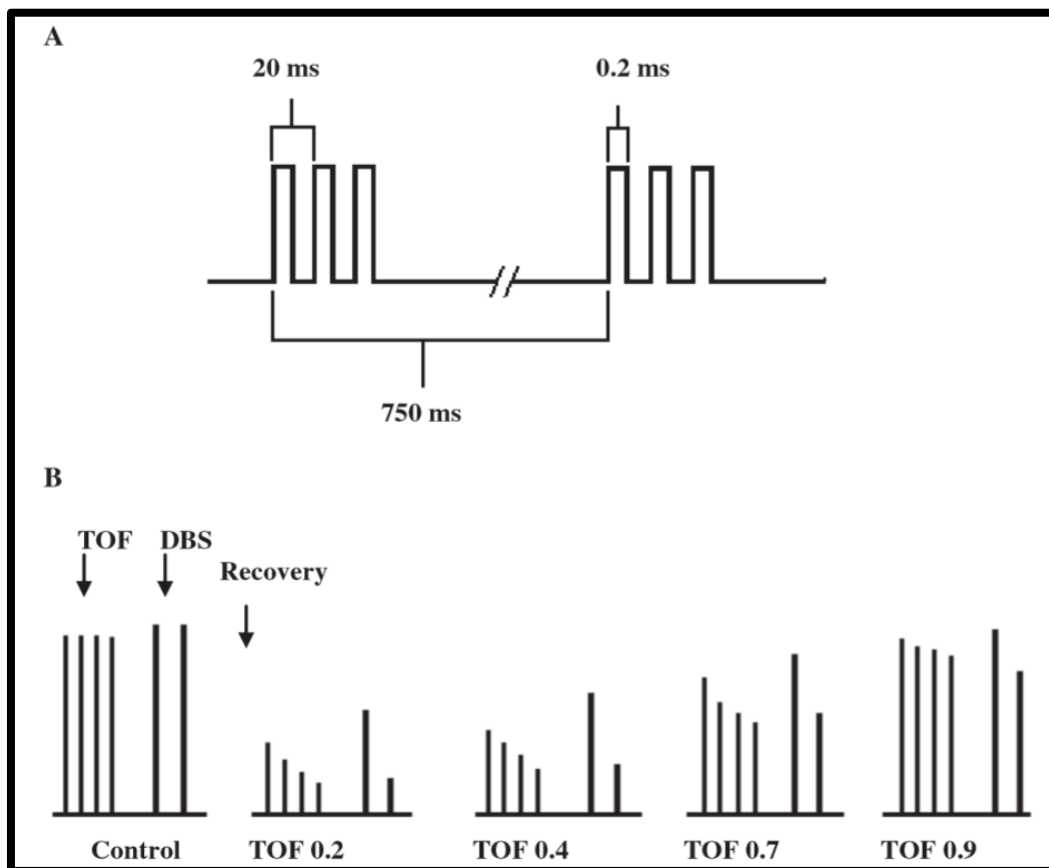
Figure 2 (A) DBS. Three impulses in each burst lasting 0.2 ms, and separated by 20 ms. The two bursts are separated by 750 ms. (B) Comparison of evoked muscle responses with DBS and TOF stimulation, after administration of a NDNMB. Fade with DBS is easier to appreciate clinically than fade with TOF stimulation. (Drenck NE, et al 1989)

In DBS, two short bursts of tetanus at 50 Hz at a supramaximal current are applied to a nerve. Typically, each burst will have three

impulses lasting 0.2 ms. Each impulse is delivered every 20 ms and the two bursts are separated by 750 ms (Fig. 4A). In unparalysed muscle, two separate muscle contractions of equal intensity will occur. In muscle partially paralysed with a nondepolarizing agent, the response to the second burst is reduced. This is the phenomenon of fade. The ratio of the magnitude of the second stimulus to the first is known as the DBS ratio. The DBS ratio has very similar properties to the TOF ratio (Fig. 4B). However, tactile evaluation of the DBS ratio has been shown to be more accurate than tactile evaluation of the TOF ratio. **(Drenck NE, et al 1989).**

Measuring evoked muscle responses

Assessing muscle responses by visual or tactile means is difficult. There are a number of mechanical (mechanomyography [MMG] and acceleromyography) and electrical (electromyography [EMG]) methods for detecting and measuring these evoked responses more accurately. **(MayO, et al 1988)**

Mechanomyography

MMG is the measurement of evoked muscle tension. The most commonly studied muscle is adductorpollicis in the thumb. **(MayO, et al 1988)**

Electromyography

EMG is the recording of a compound action potential that occurs during muscular contraction, whether voluntary or evoked. **(MayO, et al 1988)**

Acceleromyography

Acceleromyography was developed as a more convenient method of monitoring evoked responses in the operating theatre. The principle is similar to MMG; however, instead of measuring force of contraction directly, acceleration of the contracting muscle is measured. Force can then be calculated using Newton's second law of motion: force = mass x acceleration. **(MayO, et al 1988)**

Which nerve to stimulate and when?

It must be remembered that onset and offset of block is faster in central muscles with a good blood supply, for example, diaphragm and larynx. **(Donati F, 1990)**

Induction of anaesthesia

During induction of anaesthesia and tracheal intubation, the muscles of the larynx and jaw must be paralysed as well as the diaphragm. The orbicularis oculi is probably the ideal muscle to monitor at this time as it is more similar to a central muscle, onset of block will be similar to the laryngeal muscles and diaphragm. **(Donati F, 1990)**

Maintenance of anaesthesia

As the diaphragm is relatively resistant to neuromuscular block, a more sensitive peripheral muscle such as the adductor pollicis may not adequately reflect the degree of block required at this stage of anaesthesia. A central muscle which is resistant to neuromuscular block, for example, orbicularis oculi, will reflect the diaphragm more closely and should be monitored at this time. PTC and TOF monitoring are most

useful during profound neuromuscular block. **(Viby-Mogensen, et al 2000).**

Reversal and recovery

Before administering a neuromuscular antagonist, the TOF count should be at least 3. At this time, monitoring a peripheral muscle such as adductor pollicis is the best option. The respiratory muscles are likely to have recovered to a greater degree, and monitoring a peripheral muscle provides a larger margin of safety. **(Viby-Mogensen, et al 2000).**

Conditions where neuromuscular monitoring is essential

- After prolonged infusions of neuromuscular blocking drugs or when long-acting drugs are used

- When surgery or anaesthesia is prolonged

- When inadequate reversal may have devastating effects, for example, severe respiratory disease, morbid obesity

- In conditions where administration of a reversal agent may cause harm, for example, tachyarrhythmias, cardiac failure

- Liver or renal dysfunction, when pharmacokinetics of muscular relaxants may be altered

- Neuromuscular disorders such as myasthenia gravis or Eaton–Lambert syndrome. **(Viby-Mogensen, et al 2000).**

Chapter 4

Background of myopathies

Myopathy

is a disease of the muscle in which the muscle fibers do not function properly. This results in muscular weakness. Myopathy means muscle disease (Greek : myo- muscle + patheia -pathy : suffering). This meaning implies that the primary defect is within the muscle, as opposed to the nerves ("neuropathies" or "neurogenic" disorders) or elsewhere (e.g., the brain). Muscle cramps, stiffness, and spasm can also be associated with myopathy, Muscular disease can be classified as neuromuscular or musculoskeletal in nature. Some conditions, such as myositis, can be considered both neuromuscular and musculoskeletal. **(Voermans NC, et al 2009).**

Signs and symptoms

Common symptoms include muscle weakness, cramps, stiffness, and tetany. **(Voermans NC, et al 2009).**

Systemic diseases

Myopathies in systemic disease results from several different disease processes including endocrine, inflammatory, para neoplastic, infectious, drug- and toxin-induced, critical illness myopathy, metabolic, collagen related, and myopathies with other systemic disorders. Patients with systemic myopathies often present acutely or sub acutely. On the other hand, familial myopathies or dystrophies generally present in a chronic fashion with exceptions of metabolic myopathies where symptoms on

occasion can be precipitated acutely. Most of the inflammatory myopathies can have a chance association with malignant lesion; the incidence appears to be specifically increased only in patients with dermatomyositis. **(Chawla J 2011).**

There are many types of myopathy.

Inherited forms

- **Dystrophies** (or muscular dystrophies) are a subgroup of myopathies characterized by muscle degeneration and regeneration. Clinically, muscular dystrophies are typically progressive, because the muscles' ability to regenerate is eventually lost, leading to progressive weakness, often leading to use of a wheelchair, and eventually death, usually related to respiratory weakness.

- **Myotonia**

- **Neuromyotonia**

- **The congenital myopathies** do not show evidence for either a progressive dystrophic process (i.e., muscle death) or inflammation, but instead characteristic microscopic changes are seen in association with reduced contractile ability of the muscles. Congenital myopathies include, but are not limited to:

  o nemaline myopathy (characterized by presence of "nemaline rods" in the muscle),

  o multi/minicore myopathy (characterized by multiple small "cores" or areas of disruption in the muscle fibers),

o centronuclear myopathy (or myotubular myopathy) (in which the nuclei are abnormally found in the center of the muscle fibers), a rare muscle wasting disorder

- **Mitochondrial myopathies**, which are due to defects in mitochondria, which provide a critical source of energy for muscle

- **Familial periodic paralysis**

- **Inflammatory myopathies**, which are caused by problems with the immune system attacking components of the muscle, leading to signs of inflammation in the muscle

- **Metabolic myopathies**, which result from defects in biochemical metabolism that primarily affect muscle

    o Glycogen storage diseases, which may affect muscle

    o Lipid storage disorder

(Chawla J 2011).

Acquired forms

- **External substance induced myopathy**

    ❖ *Drug-induced myopathy*

      ▪ Glucocorticoid myopathy is caused by this class of steroids increasing the breakdown of the muscle proteins leading to muscle atrophy .

    ❖ *Alcoholic myopathy*

      ▪ Myopathy due to other toxic agents - including atypical myopathy in horses caused by toxins in Sycamore seeds and seedlings.

- Dermatomyositis produces muscle weakness and skin changes. The skin rash is reddish and most commonly occurs on the face, especially around the eyes, and over the knuckles and elbows. Ragged nail folds with visible capillaries can be present. It can often be treated by drugs like corticosteroids or immunosuppressants.

- *Polymyositis* produces muscle weakness. It can often be treated by drugs like corticosteroids or immunosuppressants.

- *Inclusion body myositis* is a slowly progressive disease that produces weakness of hand grip and straightening of the knees. No effective treatment is known.

- *Myositis ossificans*

- *Rhabdomyolysis and myoglobinurias*

(Seene T, 1994).

Cardio-myopathy

❖ Acute myocarditis

❖ Myocarditis in diseases classified elsewhere

❖ Cardiomyopathy

- Dilated cardiomyopathy

- Obstructive hypertrophy cardiomyopathy

- Other hypertrophic cardiomyopathy

- Endomyocardial (eosinophilic) disease

  ➢ Eosinophilic myocarditis

> ➢ Endomyocardial (tropical) fibrosis

> ➢ Löffler's endocarditis

- ▪ Endocardial fibroelastosis

- ▪ Other restrictive cardiomyopathy

- ▪ Alcoholic cardiomyopathy

- ▪ Other cardiomyopathies

❖ Arrhythmogenic right ventricular dysplasia,

(Seene T, 1994).

Differential diagnosis

At birth

- None as systemic causes; mainly hereditary

Onset in childhood

- Inflammatory myopathies – dermatomyositis, polymyositis (rarely)

- Infectious myopathies

- Endocrine and metabolic disorders – hypokalemia, hypocalcemia, hypercalcemia

Onset in adulthood

- Inflammatory myopathies – polymyositis, dermatomyositis, inclusion body myositis, viral (HIV)

- Infectious myopathies

- Endocrine myopathies – thyroid, parathyroid, adrenal, pituitary disorders

- Toxic myopathies – alcohol, corticosteroids, narcotics, colchicines, chloroquine

- Critical illness myopathy

- Metabolic myopathies

- Paraneoplastic myopathy

(Chawla J 2011).

Treatments

Because different types of myopathies are caused by many different pathways, there is no single treatment for myopathy. Treatments range from treatment of the symptoms to very specific cause-targeting treatments. Drug therapy, physical therapy, bracing for support, surgery, and massage are all current treatments for a variety of myopathies. **(Voermans NC, et al 2009).**

Chapter 5

Perioperative management of

patients with Myopathies

Patients with neuromuscular disorders (NMDs) may have altered vital functions (e.g., weakness of the respiratory muscles, scoliosis, cardiac involvement), which increase the risk of surgical procedures requiring general anesthesia (GA) or sedation. Moreover, in patients with some NMDs anesthetic agents can trigger life-threatening reactions, namely malignant hyperthermia (MH), rhabdomyolysis , or hyperkalemic cardiac arrest secondary to denervation. **(Birnkrant DJ. 2009)**

Preoperative assessment and management

Neurological assessment

pre-operative assessment must include a neurological examination to confirm the diagnosis, when feasible, and to identify the level of disease progression in each patient. some patients may lack a definite diagnosis, particularly those manifesting only with isolated elevated Creatine Kinase levels with or without minor signs. These patients are particularly at risk of life-threatening complications related to anesthesia and should be treated as highest risk level subjects. **(Klingler W, et al 2005).**

Particular situations at risk related to anesthesia

Asymptomatic preoperative elevated creatine kinase levels

- Persistent two-fold increase of CK levels merit a neuromuscular evaluation.

- Asymptomatic elevated CK levels may be the only sign of a muscle disease (e.g., muscular dystrophies at early stage, congenital

myopathies including CCD and MH, metabolic myopathies, acquired myopathies)

Subclinical Myopathy

- All patients presenting for administration of general anesthesia or sedation should be screened for motor function development

- Inability to walk past 18-months-old or other signs of motor loss or delay, especially if familiar, the presence of scoliosis or joint blocks should suggest a subclinical myopathy and should warrant neurological evaluation before elective surgery

The Myopathic Patient With Uncertain or Undefined Diagnosis

- The estimated risk of a patient with an undefined NMD to develop MH as a result of exposure to volatile anesthetic agents during muscle biopsy is very low (1.09% or less)

(Gurnaney H, et al 2009).

Pulmonary assessment

Respiratory involvement can vary significantly between different NMDs and within each disorder. Reduction of inspiratory muscle strength results initially in restrictive pulmonary impairment with a progressive decrease in forced vital capacity (FVC). Subsequently, ineffective alveolar ventilation may occur, leading to nocturnal hypercapnia and eventually to diurnal hypercapnia. In addition, weakness of expiratory muscles leads to inadequate clearance of airway secretions. Hypoventilation, coupled with an impaired cough, predisposes to atelectasis and respiratory failure.

(Gozal D. 2000)

In patients with compromised respiratory function, anesthetic agents may further decrease respiratory muscles strength, exacerbating hypoventilation, airway secretions retention, aspiration, obstructive and central apneas. These conditions may lead to nosocomial infections, prolonged intubation, tracheotomy, and eventually death. **(Wang CH, et al 2010)**

Assessment of respiratory function should include an accurate medical history and physical examination, a chest X-ray, an evaluation of sleep-disordered breathing and the measurements of respiratory function and cough effectiveness. **(Blichfeldt-Lauridsen L, et al 2012)**

Evaluation of respiratory function and cough effectiveness includes measurement of FVC, maximum inspiratory pressure, maximum expiratory pressure (MEP), peak cough flow (PCF), diurnal pulse oximetry (SpO2). SpO2 less than 95% in room air has been established as a clinically significant abnormality, requiring carbon dioxide (PCO2) level measurement. **(Bach JR, et al 2010).**

Preschool or older patients with developmental delay may not be able to perform evaluation tests of respiratory function and cough effectiveness. In these cases, the measurement of the crying vital capacity (i.e., FVC obtained from a tightly fitted mask over the nose and mouth with in line spirometer) can approximate FVC. **(Wang CH, et al 2010)**

Mechanical insufflators-exsufflator (MI-E) can increase coughing, promote deep lung inflation, and treat or prevent atelectasis. Consequently, patients with limited respiratory reserves should be trained

in these techniques before surgery and assisted with these devices during sedation, regional anesthesia and in the postoperative period. **(Tzeng AC, et al 2000)**

Recently, preoperative training in the use of NIV has been recommended for patients with Duchenne muscular dystrophy (DMD) with preoperative FVC <50% of predicted value and especially for patients at high risk of respiratory failure, defined by an FVC <30% of predicted value. Moreover, if PCF is less than 270 L/min or MEP is less than 60 cmH2O, training in assisted cough techniques is advocated before surgery. The panelists agreed that this strategy has the potential to be applied to adults and children with respiratory involvement resulting from diagnosis other than DMD. **(Birnkrant DJ, et al 2007).**

Cardiac assessment

All patients with relevant cardiac dysfunctions have a limited ability to increase cardiac output in response to stress. Consequently, they are at high risk for perioperative cardiac side effects due to negative inotropic effect of volatile and i.v. anesthetic agents, positive pressure ventilation, hypoxemia and acute anemia. **(Hopkins PM, et al 2010).**

Volatile anesthetics may also induce arrhythmia resulting from sensitization of the heart to catecholamines and from inhibitory effects on voltage-gated K^+ channels, patients with respiratory involvement leading to nocturnal hypoxemia may be affected by right ventricular changes because of pulmonary hypertension. **(Graham RJ, et al 2009)**

Table 1 Cardiac dysfunction in neuromuscular disorders. (Graham RJ, et al 2009)

Disorder	Cardiac effects
Guillain Barrè syndrome	Dysautonomia may enhance cardiovascular instability (i.e., bradycardia, blood-pressure shifts)
A subgroup of hereditary neuropathies (i.e., amyloidotic neuropathy, Shy-Drager syndromes)	Dysautonomia may enhance cardiovascular instability
Dystrophinopathies	Dilated cardiomyopathy (*very common; broad spectrum of severity including severe cardiac failure*); arrhythmias and conduction defects (*<10% of patients*)
Limb-girdle muscular dystrophies (LGMD)	Arrhythmias and conduction defects (*common*); dilated cardiomyopathy (*rare in LGMD*)
Myotonic dystrophies	Arrhythmias and conduction defects (*common*); dilated cardiomyopathy *(rare)*
Emery-Dreifuss muscular dystrophy (EDMD)	Arrhythmias and conduction defects (common); dilated cardiomyopathy
Congenital myopathies (myofibrillar myopathies)	Arrhythmias and conduction defects; dilated cardiomyopathy
Mitochondrial encephalomyopathies	Arrhythmias and conduction defects; dilated cardiomyopathy
Glycogen Storage Diseases type II	Cardiomyopathy (hypertrophic cardiomyopathy in the infantile form)
Lipid storage myopathies	Cardiomyopathy
Periodic paralysis (PP)	Cardiac arrhythmias are not common but have been reported during hyperkalemic or hypokalemic PP attacks. On the contrary, patients with Andersen syndrome are always at high risk

	for ventricular arrhythmias

In all patients, an electrocardiogram and echocardiogram should be performed before anesthesia or sedation, an electrocardiogram must be performed in all patients with periodic paralysis to exclude a long QT suggesting Andersen syndrome at risk for ventricular arrhythmias. **(Bushby K, et al 2010)**

In all patients with severe cardiac dysfunctions at least the invasive arterial pressure should be monitored during GA and in the postoperative period, In NMDs patients without primary myocardial dysfunction, preoperative cardiologic evaluation is suggested only if pulmonary hypertension is suspected. **(Graham RJ, et al 2009).**

Nutritional status should be optimized before surgery, In fact, in case of poor nutritional balance, wound healing can be delayed and the patient could be too weak to adequately clear secretions or maintain ventilation. **(Rubino FA. 2004)**

For patients chronically treated with steroids consideration has to be paid to their administration during surgery, In fact, this therapy can suppress the hypothalamic-pituitary-adrenal axis and, during a phase of stress, such as surgery, the adrenal glands may not respond appropriately, Management of surgical patients on chronic glucocorticoid therapy is very complex. Thus, it merits separate remarks. **(Blichfeldt-Lauridsen L, et al 2012)**

The preoperative evaluation should also include the assessment for a difficult intubation due to jaw ankylosis, atrophy of the masseter muscle

and/or other masticatory muscles, macroglossia or to limited mobility of the cervical spine. If any of these conditions are present, intubation should be performed taking into account adult and child guidelines for difficult airway management **(Muenster T, et al 2012).**

Moreover, obtaining an appropriate intra- venous line could be difficult in those patients. Ultrasound may assist peripheral cannulation, Besides, ultrasound-guided venous access is considered the gold standard for any patient for whom central vascular access is necessary. **(Troianos CA, et al 2012)**

In addition, patients with NMDs are predisposed to hypothermia because of reduced heat production in atrophic or dystrophic muscle. Negative effects of hypothermia are preventable by heating the skin with heated blankets or blown hot air. **(Klingler W, et al 2005)**

Preoperative considerations in specific NMDs

Myasthenia Gravis and Myasthenic syndromes

Drug therapy should be optimized. If the patient is poorly controlled, a pre-operative course of plasmapheresis or i.v. immunoglobulins could be beneficial. **(Jamal BT, et al 2009).**

Oral anticholinesterase drugs should be continued in the pre-operative period, except on the morning of surgery as they may interfere with muscle relaxants and enhance bronchial secretions. When oral administration is limited, an equivalent dosage of intravenous neostigmin should be introduced and continued until the patient resumes oral therapy. **(Nitahara K, et al 2007)**

Mitochondrial myopathies

These patients may have increased lactate levels during periods of physiological stress. Therefore preoperative fasting in these patients could be particularly hazardous. Thus, i.v. isotonic fluid containing dextrose (e.g., 0.9% sodium chloride with 5% dextrose) should be started during preoperative fasting period to allow maintenance of normoglycemia, as excessive glycolytic oxidation may increase plasma lactate levels. **(Shipton EA, et al 2004)**

Intraoperative management

In NMDs patients with decreased pulmonary function GA should be avoided preferring regional anesthesia whenever possible. If GA is unavoidable, ultra short acting drugs, such as propofol and remifentanil, are preferable and succinylcholine must be avoided. Furthermore, administration of volatile anesthetics in myopathic patients is usually considered at high risk for life-threatening complications. **(Schmiesing CA, et al 2010).**

Succinylcholine and halogenated agents

In motor neuron and peripheral nerve diseases the use of halogenated agents is permitted, whereas succinylcholine must be avoided**. (Kapur S, et al 2007)**

In patients with neuromuscular junction disorders, GA can be performed using halogenated agents. **(Klingler W, et al 2005)**

In myopathic patients the use of inhaled anesthetics and succinylcholine is classically considered at high risk for MH or acute rhabdomyolysis. **(Veyckemans F. 2010)**

Total intravenous anesthesia (TIVA)

If inhalation anesthesia has to be avoided, GA can be performed using TIVA, it should be minded that respiratory and cardiac depression can be induced by intravenous anesthetic agents and opioids. Thus, the dose of these drugs should be carefully titrated to be effective. **(Bisinotto FM, et al 2010).**

Although the effectiveness of target controlled infusion (TCI) of propofol compared with manually controlled infusion remains controversial in adults and in children, some authors reported that careful titration of propofol by TCI enables to evaluate the patient's sensitivity to propofol in subjects with NMDs. **(Morimoto Y, et al 2005).**

Moreover, despite its well-known limitation in pediatric patients the use of Bispectral Index Monitor (BIS) may prevent the occurrence of awareness and reduce the risk of drugs' overdose in patients with NMDs. **(Ganesh A, et al 2004).**

Non-depolarizing neuromuscular blocking agents (NMB)

In all patients with NMDs, non-depolarizing NMB may show prolonged duration of neuromuscular blockade even when short-acting. Thus, most reports recommend avoidance of NMBs whenever possible. **(Lee D, et al 2008)**

when NMB are necessary, the dose should be reduced and titrated to effect, neuromuscular function has to be continuously monitored (e.g., using the train-of-four monitoring), and the effect of muscle relaxant should be antagonized. **(de Boer HD, et al 2009)**

Nevertheless, anticholinesterase drugs are not recommended because they may lead to hyperkalemia, reversal of rocuronium-induced or vecuronium-induced neuromuscular blockade by sugammadex could

be beneficial in NMDs to eliminate the risk of postoperative residual muscle paralysis, Finally, the combination of rocuronium and sugammadex could replace the need for succinylcholine in rapid sequence induction in patients with NMDs. **(Unterbuchner C, 2010)**

Regional anesthesia

There are potential risks with regional anesthesia in patients with preexisting peripheral nervous system diseases. Upton and McComas emphasized that if these patients are exposed to secondary damages such as injuries from needles or catheters, ischemic lesions from vasopressors, or toxicity of a local anesthetic, the probability of neurological damages increases. **(Upton AR, et al 1973)**.

On the other hand, the use of regional or local anesthesia offers a significant advantage in term of avoidance of anesthetic drugs and reduction of postoperative respiratory complications for all patients with NMDs and mainly in those with reduced pulmonary function. **(Gross JB, et al 2006)**.

A significant reduction of the required volume of local anesthetic is possible when ultrasound or peripheral nerve stimulator are used for nerve identification, the use of ultrasound appeared to reduce the incidence of hematoma formation following vascular puncture. **(Walker KJ, 2009)**.

Table 2 Overview of anesthetic strategies in neuromuscular diseases (Driessen JJ. 2008)

Neuromuscular diseases	Regional anestesia	Volatile anesthetic drugs	Succinylcholine	NDMR	Opioids	Other issues
Spinal muscular atrophy	YES	YES	NO	↓+M or avoided	↓	
Amyotrophic lateral sclerosis	YES	YES	NO	↓+M or avoided	↓	
Guillain Barrè Syndrome	YES	YES	NO	↓+M or avoided	↓	– Anesthesia may be associated with severe complications due to dysautonomia.
Myasthenia gravis	YES	YES	↑	↓+M or avoided	↓	–Administer AChE slowly and cautiously –Sugammadex should be considered –Factors which can enhance neuromuscular blockade should be avoided
Lambert–Eaton syndrome	YES	YES	↓	↓+M or avoided	↓	– Factors which can enhance neuromuscular blockade should be avoided
Duchenne and Becker muscular dystrophy and other progressive muscular dystrophies	YES	NO	NO	↓+M or avoided	↓	– Avoid AChE –Sugammadex should be considered
Myotonic dystrophy	YES	controversial	NO	↓+M or avoided	↓	–There is an increased sensi- tivity against thiopental and propofol –Prevent myotonia avoiding AChE, hypothermia, electri- cal scalpel, dyskalaemia, propranolol
Congenital myopathies	YES	NO	NO	↓+M or avoided	↓	
Congenital muscular dystrophies	YES	controversial	NO	↓+M or avoided	↓	
Mitochondrial myopathy	YES	YES	NO	↓+M or avoided	↓	–Thiopental and propofol interfere with mitochondrial function. – Avoid prolonged use of pro- pofol. Prevent lactic acidosis avoiding hypoglycemia, hypoxia, hypotension
Glycogen storage disease	YES	NO	NO	↓+M or avoided	↓	

YES: may be used or should be performed; NO: it is contraindicated; ↓, dose should be decreased; ↑, dose should be increased; M: muscle relaxation monitor must be used; AChE: anticholinesterase drugs; NMDR: non-depolarizing muscle relaxants.

Anesthetic considerations in specific NMDs

Guillain-Barrè Syndrome (GBS)

in patients with GBS, anesthesia may be associated with severe complications due to dysautonomia (i.e., bradycardia, blood-pressure swings, and profound hypotension with sedatives). In patients with autonomic dysfunction, a potential sympathetic blockade resulting from regional anesthesia requires careful control of blood pressure. Consequentially, a neuraxial blockade should be cautiously administered to patients with GBS. However, several cases have been reported in which epidural and spinal anesthesia were successfully used without haemodynamic instability. **(Vassiliev DV, et al 2001)**

Myasthenia Gravis (MG) and Myasthenic Syndromes

Factors potentially enhancing neuromuscular blockade should be avoided (e.g. hypothermia, hypokalemia, hypophosphatemia and several drugs) As local anesthetic agents may block neuromuscular transmission, subarachnoid and epidural anesthesia should be performed using reduced doses and preferably amid local anesthetics, such as bupivacaine and ropivacaine. **(Blichfeldt-Lauridsen L, et al 2012).**

Excess of anticholinesterase drugs may produce flaccid muscle paralysis and pupil constriction (cholinergic crisis) in patients with MG, intravenous anticholinesterase drugs should be administered slowly and cautiously in the postoperative period. Moreover, meticulous attention to pulmonary toilet is required, particularly since respiratory secretions may be increased by the anticholinesterase drugs. **(Hirsch NP. 2007)**

Sugammadex, in combination with neuromuscular monitoring, can be used to reverse rocuronium-induced neuromuscular blockade in

patients with MG, thereby avoiding the need for reversal with acetylcholinesterase inhibitors. **(Unterbuchner C, et al 2010).**

Dystrophinopathies

Several studies have shown a delayed onset of nondepolarizing muscle relaxants in patients with dystrophinopaties. Therefore, a high dose of rocuronium is needed to shorten the onset time. Reversal of NMB by sugammadex will eliminate the risk of postoperative residual paralysis, even after a high-dose of rocuronium. **(de Boer HD, et al 2009).**

Myotonic dystrophy

Peripheral nerve or neuroaxis blockade are preferable. When GA is indicated, extreme care should be taken during all phases of anesthesia. Many authors have proposed the use of halogenated gases in these patients but others consider safer to avoid them. Noteworthy, halogenated agents may induce postoperative shivering which can precipitate myotonia.   **(Parness J, et al 2009).**

Thiopental is relatively contraindicated due to prolonged respiratory depression. Propofol can be successfully used both for induction and maintenance of anesthesia, if the dose is carefully titrated. **(Weingarten TN, et al 2010)**

The development of myotonia represents an important problem for anesthesia because, if laryngeal and respiratory muscles are involved, intubation can be difficult or even impossible, Myotonia occurs for an intrinsic change in the muscle and not in the peripheral nerve or neuromuscular junction. Thus, it cannot be abolished by peripheral nerve blockades or neuromuscular blockers. Myotonia may be treated with

midazolam, otherwise the treatment is mainly preventive, avoiding all triggering factors. **(Bisinotto FM, et al 2010).**

The use of electrical scalpel, dyskalemia, triggering drugs and an excessive stress should be avoided, body temperature should be closely monitored to minimize the risk of shivering, and succinylcholine should not be administrated. **(Allison KR. 2007)**

Finally, these patients have also a propensity to develop hyperglycemia, dysphagia and gastro- esophageal reflux. Maintaining the torso of the patient elevated in the postoperative period re duces the risks of aspiration. **(Bisinotto FM, et al 2010).**

Periodic paralysis

Precipitant factors of attacks in hyperkalemic periodic paralysis include anesthesia, cold exposure and fasting. Therefore, after recovering from general anesthesia, patients with this disorder may be paralyzed for hours. Moreover, opioids or succinylcholine can precipitate a myotonic reaction that may interfere with intubation and ventilation. Finally, prevention of carbohydrate depletion and avoidance of muscle relaxants are recommended in this setting. **(Klingler W, et al 2005).**

Mithocondrial myopathies

The mitochondrial myopathies consist of a heterogeneous group of disorders caused by abnormalities in mitochondria leading to muscle weakness, lactic acidosis and a variable combination of the central and/or peripheral nervous system involvement (seizures, hemiparesis, cortical blindness, ophthalmologic abnormalities, hearing loss), bulbar dysfunction with impaired swallowing, cardiac dysfunction, hepatic and renal disease, defect of insulin secretion. **(Driessen JJ. 2008)**

Propofol has a mitochondrial depressant effect that can induce lactic acidosis. Moreover, in these patients also other anesthetic agents such as thiopentone, midazolam, halogenated agents and local anesthetics can cause lactic acidosis interfering with mitochondrial function. Nevertheless, it is noted that all these anesthetic agents have been used with success in patients with mitochondrial myopathies. **(Driessen JJ. 2008)**

However, caution is required with all anesthetic agents, it would be seen as pertinent to avoid the prolonged use of propofol for the maintenance of anesthesia, lactic acidosis should be prevented with control of excessive stress, maintaining normal serum glucose levels, adequate oxygen balance, stable cardiovascular function, and adequate gas exchange, the routine perioperative use of lactate- free i.v. fluids in all patients with mitochondrial disease undergoing GA is recommended. **(Shipton EA, et al 2004)**

Glycogenosis type II (GSDII)

In the infantile form of GSDII, characterized by a significant hypertrophic cardiomyopathy, decreased cardiac output and myocardial ischemia have been observed during anesthesia, stiffness of the hypertrophied ventricular walls can induce abnormal diastolic relaxation and lead to dynamic left ventricular outflow tract obstruction, elevated left ventricular end-diastolic pressure and reduced diastolic filling. **(Bembi B, et al 2008).**

Life-threatening complications related to anesthesia in neuromuscular disorders

Malignant Hyperthermia (MH)

Rare inherited drug-induced disorder of the skeletal muscle characterized by an increased muscle metabolism with excessive heat, carbon dioxide and lactate production, high oxygen consumption, contractures of the muscles and myofiber breakdown, usually triggered when an MH-susceptible individual is exposed to a halogenated agents or succynilcholine and in rare cases to strenuous exercise and/or heat exposure. **(Wappler F. 2010)**

Patients at risk

- Diagnosis of RYR1 mutations or CCD

- Relatives of MH or CCD patients

- Few muscle diseases:

  - Central core disease (CDC)

  - Core-rod myopathy

  - King–Denborough syndrome

(Wappler F. 2010)

Management of Acute Crisis

- Discontinue inhalational agents and use non-triggering agents for the remainder of the procedure

- Hyperventilate with 100% oxygen and intubate with endotracheal tube

- Give dantrolene: loading bolus of 2.5 mg/kg i.v., with subsequent bolus doses of 1 mg/kg i.v. until the signs of acute MH have abated; 1 mg/kg every 6 hours should continue for 48 hours after the last observed sign of acute MH to prevent recrudescence

- Give sodium bicarbonate for acidosis

- Cool the patient: cold saline for infusion; ice to body surface; lavage body cavities (eg, stomach, bladder, rectum). Maintain temperature <39°C

- **Treat hyperkalemia:**

  ➤ to antagonize the myocardial effects of hyperkalemia give immediately calcium chloride IV (repeat the dose after 5 minutes if ECG changes persist)

  ➤ to shift potassium back into muscle cells hyperventilate, give sodium bicarbonate and insulin with 10% dextrose (monitor finger stick glucose closely)

- Treat dysrhythmias: usually responds to treatment of acidosis and hyperkalemia; use standard ACLS protocols; calcium channel blockers are contraindicated in the presence of dantrolene.

(US MHAo. 2010)

Rhabdomyolysis

It's an uncommon but potentially fatal disorder triggered by succynilcholine or halogenated agents in susceptible patients, characterized by muscle necrosis with release of intracellular muscle constituents (i.e. myoglobin, potassium and creatine kinase) into the circulation. It can be acute, resulting in hyperkalaemic cardiac arrest or subacute, presenting as dark urine or cardiac arrest in the postanaesthesia care unit. **(Wappler F. 2010)**

Patients at risk

- Succynilcholine may cause rhabdomyolysis in almost all neuromuscular diseases, but especially if muscles are denervated, progressively dystrophic or metabolically altered.

- Halogenated agents may cause rhabdomyolysis in patients with myopathies (especially dystrophinopathies and metabolic myopathies)

(Wappler F. 2010)

Management of Acute Crisis

- Treat hyperkalemia (see malignant hyperthermia)

- Prevent heme pigment-induced acute kidney injury:

  ➢ early and aggressive fluid resuscitation with isotonic saline to maintain the urine output greater than 1 mL/Kg/hour

  ➢ loop diuretics may be given to patients who develop volume overload as a result of aggressive volume administration

➢ alkalinization of urine: administration of an alkaline solution to maintain the urine pH above 6.5, providing the patient is not severely hypocalcemic, and has an arterial pH less than 7.5 and a serum bicarbonate less than 30 meq/L.

- Treat acute kidney injury: dialysis may be necessary for control of hyperkalemia and correction of acidosis, or for the treatment of volume overload.

(Hayes J, 2008)

Hyperkalemic Cardiac Arrest Secondary to Denervation

Cardiac arrest due to hyperkalemia triggered by succynilcholine in the presence of striated muscle denervation hypersensitivity (upregulation of nicotinic acethylcholine receptors) **(Schmitt HJ, et al 2009)**

Patients at risk

- Motor neuron diseases

- Peripheral neuropathies

(Schmitt HJ, et al 2009)

Management of Acute Crisis

- Use standard ACLS protocols

- To shift potassium back into muscle cells, give sodium bicarbonate, insulin with 10% dextrose and hyperventilate

- Continue cardiopulmonary resuscitation until serum potassium levels are lowered to a near normal level

(Driessen JJ. 2008)

Postoperative management

Pain control

Adequate pain control is essential to prevent hypoventilation secondary to splinting after thoracic, upper abdominal and spine surgery, Intravenous opioids should be titrated to provide adequate analgesia and promote airway clearance minimizing respiratory suppression. This goal is best accomplished with preemptive analgesia and using multiple pharmacological agents.**(Wang CH, et al 2010)**

Oral clonidine administered preoperatively has been shown to reduce the requirement for postoperative analgesics. Moreover, i.v. paracetamol, administered alone or in combination with nonsteroidal anti-inflammatory agents (e.g., ketorolac), has been shown to reduce the amount of opiates delivered.**(Hidalgo MP, 2005)**

Continuous infusion of opioids via epidural catheters can be used when appropriate to achieve pain control while minimizing respiratory side effects. **(Tobias JD. 2004).**

Finally, wound infiltration with local anesthetic solutions and continuous infusion of local anesthetic solutions via peripheral nerve block catheters should be offered when appropriate as safer alternative. **(Graham RJ, et al 2009)**

Peripheral nerve blocks have been shown to provide postoperative analgesia which is comparable to that obtained with an epidural technique but with less side-effects, using ultrasound guidance or nerve stimulation techniques. **(Walker KJ, 2009).**

Neuropathic deep pain and dysesthetic burning pain that frequently occurs in Guillain-Barre'Syndrome may be treated using gabapentin. In patients admitted to ICU not responding to treatment with gabapentin, remifentanil infusion can provide a satisfactory analgesia. **(Johnson DS, 2008)**

In case of hypoventilation after opioid administration, adequate ventilation can be achieved by using NIV or by delaying extubation for 24 to 48 hours. **(Birnkrant DJ, et al 2007).**

Respiratory management

Postoperative management should be determined by preoperative respiratory function and the type of surgery performed. Patients with normal cough clearance and relatively preserved muscle function are not at increased risk for postoperative complications. On the other hand, patients with decreased respiratory muscle strength require close monitoring and aggressive respiratory management. **(Birnkrant DJ, et al 2007).**

The application of a protocol based on the combination of NIV with MI-E after extubation for high-risk NMDs patients, may provide a clinically important advantage by averting the need for reintubation or tracheotomy and shortening their ICU stay. **(Wang CH, et al 2010)**

Extubation directly to NIV should be considered for patients with baseline FVC <50% of predicted, and should be strongly considered for those with FVC <30% of predicted. Postoperatively use of assisted cough techniques including the use of MI-E must be considered for any teenage or adult with preoperative PCF <270 L/min or MEP <60 cm H2O. **(Almenrader N, et al 2006)**

To maximize the chance of success, extubation should be delayed until respiratory secretions are well controlled and SpO2 is normal or baseline in room air. **(Niranjan V, et al 1998)**

In patients requiring long-term mechanical ventilation (e.g., patients with Guillain- Barre'Syndrome) respiratory support must be continued in the postoperative period. **(Tonelli D, et al 2005)**

Oxygen must be applied with caution in NMDs patients because it can correct hypoxemia without treating the underlying cause such as hypercapnia, mucus plugging and atelectasis. To facilitate appropriate oxygen use, CO_2 levels should be monitored. **(Niranjan V, et al 1998)**

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Summary

The anaesthetic management of patients with myopathies is challenging. Considering the low incidence and heterogeneity of these disorders, most anaesthetists are unfamiliar with key symptoms, associated co-morbidities and implications for anaesthesia.

The pre-anaesthetic assessment aims at the detection of potentially undiagnosed myopathic patients and, in case of known or suspected muscular disease, on the quantification of disease progression. Ancillary testing (e.g. echocardiography, ECG, lung function testing etc.) is frequently indicated, even at a young patient age

one must differentiate between myopathies associated with malignant hyperthermia (MH) and those that are not, as this has significant impact on preoperative preparation of the anaesthesia work station and pharmacologic management

Only few myopathies are clearly associated with MH. If a regional anaesthetic technique is not possible, total intravenous anaesthesia is considered the safest approach for most patients with myopathies to avoid anaesthesia-associated rhabdomyolysis. However, the use of propofol in patients with mitochondrial myopathies may be problematic, considering the risk for propofol-infusion syndrome.

Succinyl choline is contra-indicated in all patients with myopathies. Following an individual risk/benefit evaluation, the use of volatile anaesthetics in several non-MH-linked myopathies (e.g. myotonic syndromes, mitochondrial myopathies) is considered to be well tolerated. Perioperative monitoring should specifically focus on the cardiopulmonary system, the level of muscular paralysis and core

temperature. Given the high risk of respiratory compromise and other postoperative complications, patients need to be closely monitored postoperatively.

الملخص العربي

ان الاعتلال العضلي مرض تصاب به العضله بعيدا عن التغذية العصبية العضلية او الاتصال العصبي العضلي وذلك لاسباب عديده منها ماهوبسبب عيب خلقي اومكتسب اوليس له سبب واضح اونتيجة عدوي اوخلل في التمثيل الغذائي او نتيجة التهابات اوخلل في الهرمونات اوبسبب تناول بعض الادوية .

يصاب مرضي الاعتلال العضلى بخلل في الوظائف الحيوية كضعف عضلات التنفس وتشوهات العمود الفقرى وضعف عضلة القلب مما يؤدي ذلك الي زياده نسبة خطورة العمليات الجراحية التي تتطلب تخدير كلى او تهدئة هؤلاء المرضي .

ان لبعض المواد المخدرة دور في اثارة بعض التفاعلات الخطرة التي تهدد حياه المرضي المصابين بالاعتلال العضلى كارتفاع درجة الحراره الخبيث وانحلال الربيدات وارتفاع نسبة البوتاسيوم في الدم التي تؤدي الي توقف عضلة القلب نتيجة ازالة التعصيب. ان تخديرمرضي الاعتلال العضلي امرمثيرللتحدي ولذلك تهدف عملية تقييم المريض قبل تخديره الي اكتشاف المرضى الذين لم يتم تشخيصهم ومعرفة مدي تطور المرض .

يعتبر التشخيص المفصل للمرض امر ضرورى ليتم تقدير مدي الخطورة اثناء العملية الجراحية او التخدير ولذلك تقييم المريض قبل الجراحة لابد ان يشمل فحص الجهاز العصبي للتاكد من تشخيص المرض ولاي مدى وصل اليه المرض

ان تقييم الوظائف التنفسية للمرضي لابد ان يشمل المعرفة الدقيقة للتاريخ المرضي والفحص الطبي واجراء بعض الفحوصات كاشعة اكس للصدر وتقييم مشاكل التنفس اثناء النوم وقياس وظائف التنفس وفعالية السعال.

من الضروري ان يخضع مرضي الاعتلال العضلي الى تقييم دقيق لوظائف القلب وضبط الخطة العلاجية قبل التخدير كرسم القلب والاشعة التليفزيونية علي القلب اذا لم يتم اجرائها خلال اثنى عشر شهرا

يهدف تقييم المريض المصاب بالاعتلال العضلي داخل غرفة العمليات الي تجنب التخدير الكلي وتفضيل التخديرالموضعي قدر المستطاع وان كان التخدير الكلي ضرورة لايمكن تجنبها فلابد من استخدام الادويه قصيرة المدي مثل عقار البروبوفول والريميفنتايل وتجنب السكسينيل كولين والاستنشاق التخديري وذلك لخطورتها علي حياة المريض.

تهدف متابعة المريض بعد الجراحة الي المتابعة الدقيقة لوظائف التنفس عن طريق القضاء علي الالم مابعد عمليات الصدر وجراحات البطن او جراحات العمود الفقري لاثرها علي عملية التنفس.

ان مرضي الاعتلال العضلي معرضون لمخاطر كثيرة اثناء العملية الجراحية وما بعدها اكثر من غيرهم من المرضي ولذلك يجب وضع خطة مسبقة ومحكمة ومتعددة التخصصات قبل اجراء عملية التخدير لاي جراحة وذلك يجب ان يكون داخل مستشفي مجهزة وعلي درجة عالية من الخبرة للتعامل مع مثل هذه الحالات المرضية.

المعالجة التخديرية للمرضى المصابين بالإعتلال العضلي

توطئة للحصول على درجة الماجستير في التخدير

مقَدمة من

الطبيب /غادة احمد سعد الدين

بكالوريوس الطب والجراحة

كلية الطب

جامعة بنها

تحت اشراف

الاستاذ الدكتور/ ايهاب الشحات عفيفي

استاذ التخدير والعناية المركزة

كلية الطب - جامعة بنها

الدكتور/ محمد فؤاد المليجي

مدرس التخدير والعناية المركزة

كلية الطب - جامعة بنها

كلية الطب

جامعة بنها

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