REVIEW

Recommendations for anesthesia and perioperative management of patients with neuromuscular disorders

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ABSTRACT

Patients with neuromuscular disorders are at high risk of intraoperative and postoperative complications. General anesthesia in these patients may exacerbate respiratory and cardiovascular failure due to a marked sensitivity to several anesthetic drugs. Moreover, succinylcholine and halogenated agents can trigger life-threatening reactions, such as malignant hyperthermia, rhabdomyolysis and severe hyperkalemia. Therefore, regional anesthesia should be used whenever possible. If general anesthesia is unavoidable, special precautions must be taken. In particular, for patients at increased risk of respiratory complications (*i.e.,* postoperative atelectasis, acute respiratory failure, nosocomial infections), noninvasive ventilation associated with aggressive airway clearance techniques can successfully treat upper airway obstruction, hypoventilation and airway secretion retention, avoiding prolonged intubation and tracheotomy. Anesthesia and perioperative management of patients with neuromuscular disorders are described in this article. To grade the strength of recommendations and the quality of evidence we adopted the GRADE approach. In case of low-quality evidence, these recommendations represent the collective opinion of the expert panel. *(Minerva Anestesiol 2013;79:419-33)*

Key words: Anesthesia - Neuromuscular diseases - Noninvasive ventilation - Insufflation.

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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.[1-5] Moreover, in patients with some NMDs anesthetic agents can trigger life-threatening reactions,[6-8, 9] namely malignant hyperthermia (MH),[10-14] rhabdomyolysis [10, 12-14] or hyperkalemic cardiac arrest secondary to den-

Table I.—*Life-threatening complications related to anesthesia in neuromuscular disorders.*

MALIGNANT HYPERTHERMIA (MH)	RHABDOMYOLYSIS	HYPERKALEMIC CARDIAC ARREST SECONDARY TO DENERVATION

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
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
	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
	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)
		Cardiac arrest due to hyperkalemia triggered by succynilcholine in the presence of striated muscle denervation hypersensitivity (upregulation of nicotinic acethylcholine receptors)
		Patients at risk
		- Motoneuron diseases
		- Peripheral neuropathies

PREVENTION OF LIFE-THREATENING COMPLICATIONS RELATED TO ANESTHESIA

a) **Choice of anesthesia**: 'trigger-free' anesthetic and 'clean' anesthesia machine for halogenated agents if it's pertinent. Anesthesia machine must be prepared by using a disposable circuit, a fresh CO2-absorbent, disconnecting the vaporisers and flushing with O2 at a rate of 10 l min for at least 20 min before use. However, these recommendations are derived from older style anesthetic machines and modern anesthetic workstations may need longer cleaning times to wash out residual inhalational anesthetics in order to establish an acceptable concentration below 5 parts per million

b) **Availability of sufficient quantities of dantrolene** in order to treat MH: dantrolene (vials: 20 mg each)

c) **Adequate intra and post-operative monitoring:** carefully monitoring for signs of rhabdomyolysis up to 12 hrs postoperatively (i.e. serial plasma CK and myoglobin and urine myoglobin), capnometry, and continuous measurement of body temperature

MANAGEMENT OF ACUTE CRISIS

MALIGNANT HYPERTERMIA
- 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

RHABDOMYOLYSIS
- 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

HYPERKALEMIC CARDIAC ARREST
- 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

MH: malignant hyperthermia; CCD: central-core disease; CK: creatine kinase.

ervation (Table I).[7, 13, 15, 16] On the other hand, survival rates of these patients has progressively improved, increasing the need for surgical procedures related or unrelated to NMDs.[17]

This article will review the assessment and management of patients with NMDs before, during, and after GA or sedation. Because literature addressing this topic is restricted by the small number of patients and randomized trials are scarce, the document represents a collection of statements based on expert opinion and literature review.

Materials and methods

In January 2011, a group of physicians met to discuss current clinical care issues for patients with NMDs undergoing anesthesia. This core committee appointed two chairmen with expertise in NMDs (Toscano and Racca) and later invited a group of Italian experts to form a panel of 43 members from 8 medical subspecialties. The committee's mission was to review the anesthesia and perioperative management of patients with NMDs. Scientific expertise was the first criteria to select the panelists. However, to ensure geographic diversity, other panelists were chosen with specific clinical expertise. This may represent a minor limitation of this document. The most relevant literature was identified by querying PubMed (www.pubmed.gov) from January 1991 to September 2011, and including only human studies. We used the search terms "neuromuscular diseases", "muscular dystrophy", "myopathy", "myasthenia", "rhabdomyolysis", "malignant hyperthermia", cross-referenced with the term "anesthesia". We identified 252 articles as relevant to the document between 2645 recovered articles. We used an informal consensus technique involving group discussions moderated by a chairperson and conducted in-person during a roundtable meeting (Torino, October 7, 2011), that was organized with the financial support of SIAARTI. All suggested statements were presented and voted by the panel experts during a plenary roundtable. Consensus was demonstrated by unanimous consent around presented options. To grade the strength of recommendations and the quality of evidence we adopted the GRADE approach (Table II).[18]

Preoperative assessment and management

Neurological assessment

Detailed diagnosis is essential to assess the risk during surgery and anesthesia. Thus, preoperative assessment must include a neurological examination to confirm the diagnosis, when feasible, and to identify the level of disease progression in each patient.[13] However, diagnostic process may be complex and 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 (Table III) (Grade 1C).[19-106]

Table II.—*A summary of GRADE's approach to rating quality of evidence and strength of recommendation.*

Recommendation grades
1. Strong recommendation: benefits clearly outweigh the risks and burdens for most, if not all, patients
2. Weak recommendation: benefits and risks closely balanced and/or uncertain

Evidence grades
A. High-quality evidence: consistent evidence from randomized trials, or overwhelming evidence of some other form
B. Moderate-quality evidence: evidence from randomized trials with important limitations, or very strong evidence of some other form
C. Low-quality evidence: evidence from observational studies, unsystematic clinical observations, or from randomized trials with serious flaws

Grade 1A. Strong recommendation. High quality evidence.
Grade 1B. Strong recommendation. Moderate quality evidence.
Grade 1C. Strong recommendation. Low quality evidence.
Grade 2A. Weak recommendation. High quality evidence.
Grade 2B. Weak recommendation. Moderate quality evidence.
Grade 2C. Weak recommendation. Low quality evidence.

Table III.—*Particular situations at risk related to anesthesia.*

1) ASYMPTOMATIC PREOPERATIVE ELEVATED CREATINE KINASE LEVELS
– Persistent two-fold increase of CK levels merit a neuromuscular evaluation [104]
– 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) [106]
– The use of halogenated agents and succinylcholine should be considered with caution unless these diagnoses are excluded[8]
– If so the use of TIVA or regional anesthesia, whenever possible, should be planned to decrease life-threatening complications related to anesthesia (Grade1C)
– However, if mitochondrial disease is a concern (high lactate, multiple organ involvement), propofol should be used for induction only and halogenated agents can be used [8, 15]
2) SUBCLINICAL MYOPATHY
– All patients presenting for administration of general anesthesia or sedation should be screened for motor function development [11, 36]
– 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
3) 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) [105]
– The use of loco-regional anesthesia should be considered whenever possible [15]
– The use of succinylcholine must be avoided [15]
– The use of halogenated agents must be avoided.[15, 19] They should only be used briefly for induction until an intravenous catheter is placed, or when higher risks such as a difficult airway exist.[15, 105] Then, immediate conversion to TIVA and a clean anesthesia machine is recommended, and the child should be carefully monitored for signs of rhabdomyolysis because, even if the risk is low, its occurrence is unpredictable [12]
– However, if mitochondrial disease is a concern (high lactate, multiple organ), propofol should be used for induction only and halogenated agents can be used [8, 15]
– For minor surgery such as muscle biopsy in children, ketamine may be a safe alternative to propofol and halogenated agents

CK: creatine kinase; CCD: central-core disease; TIVA: total intravenous anesthesia; MH: malignant hyperthermia; NMD: neuromuscular disorders.

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.[6] 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. Furthermore, patients with NMDs often experience mild to moderate bulbar dysfunction, affecting their ability to swallow. Patients with type 1 spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), myasthenia gravis (MG) and with other rapidly progressive NMDs may develop a more severe bulbar dysfunction with an increased likelihood of aspiration.[19-22] Finally, respiratory status can be further impaired by sleep apneas, nutritional problems, gastro-esophageal reflux or progressive scoliosis.

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. Therefore, in all patients with NMDs preoperative pulmonary evaluation is strongly recommended to assess the risk of respiratory complications and the need of specific perioperative and postoperative management (Grade 1C).[1, 4, 5, 20, 21, 23-26]

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.[2, 4, 5, 20, 21] 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 (SpO_2). SpO_2 less than 95% in room air has been established as a clinically significant abnormality, requiring carbon dioxide (PCO_2) level

measurement.[2, 4, 5, 19, 27-29] 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.[4]

It is crucial to optimize the patient's respiratory status before surgery. When respiratory function measurements and/or sleep studies are abnormal, non-invasive ventilation (NIV) and manual or mechanically assisted cough techniques may be indicated. Therefore, planning and coordination with the hospital respiratory therapists is crucial. In particular, mechanical insufflators-exsufflator (MI-E) can increase coughing, promote deep lung inflation, and treat or prevent atelectasis.[27-33] 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 (Grade 1C).[2, 4, 5, 22, 24, 25, 34] This strategy is also recommended for patients already using assisted cough and long term NIV (Grade 1C).[5]

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.[1, 2] Moreover, if PCF is less than 270 L/min or MEP is less than 60 cmH_2O, training in assisted cough techniques is advocated before surgery.[1, 2] 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.[1]

Cardiac assessment

Several NMDs are associated with cardiac dysfunctions (cardiomyopathies and/or abnormality of the conduction system) as shown in Table IV. However, clinical manifestations of heart failure are often unrecognized until very late, owing to musculoskeletal limitations.[3, 35]

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.[36] Volatile anesthetics may also induce arrhythmia resulting from sensitization of the heart to catecholamines and from inhibitory effects on voltage-gated K^+ channels.[13] Finally, NMDs patients with respiratory involvement leading to nocturnal hypoxemia may be affected by right ventricular changes because of pulmonary hypertension.[16]

Table IV.—*Cardiac dysfunction in neuromuscular disorders.*

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 type 2A, 2D*)
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

Therefore, those patients should undergo a careful assessment of heart function as well as optimization of cardiac therapies before anesthesia or sedation (Grade 1C).[7] In all patients, an electrocardiogram and echocardiogram should be performed before anesthesia or sedation, if not done in the previous 12 months.[3, 35] In particular, an electrocardiogram must be performed in all patients with periodic paralysis to exclude a long QT suggesting Andersen syndrome at risk for ventricular arrhythmias. Moreover, signs or symptoms of arrhythmias should be promptly investigated with a Holter test.[3, 35] In addition, patients with a high degree of AV blocks may need a cardiac pacemaker before GA.

In all patients with severe cardiac dysfunctions at least the invasive arterial pressure should be monitored during GA and in the postoperative period (Grade 2C).[24]

In NMDs patients without primary myocardial dysfunction (*e.g.*, SMA), preoperative cardiologic evaluation is suggested only if pulmonary hypertension is suspected.[16]

Other issues

Nutritional status should be optimized before surgery.[2, 4, 20] 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 (Grade 2C).[4]

Patients with NMDs have an increased sensitivity to premedication drugs, which could induce sleep apnea and hypoventilation.[37]

For patients chronically treated with steroids (*i.e.*, DMD, MG) consideration has to be paid to their administration during surgery.[21, 38] 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.[39] Management of surgical patients on chronic glucocorticoid therapy is very complex. Thus, it merits separate remarks.[40-42]

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.[2, 5, 15, 16, 37] If any of these conditions are present, intubation should be performed taking into account adult [43] and child [44] guidelines for difficult airway management (Grade 1C).

Moreover, obtaining an appropriate intravenous line could be difficult in those patients. Ultrasound may assist peripheral cannulation.[45] Besides, ultrasound-guided venous access is considered the gold standard for any patient for whom central vascular access is necessary.[46] In this case, a peripherally-inserted central venous catheter utilizing a cephalic or basilic venous approach under ultrasonic guidance, may provide a safe alternative to the standard approach (Grade 1C).[47]

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 (Grade 2C).[13]

Postoperative admission to an intensive care unit (ICU) should be considered in any patient at risk for respiratory complications, with weak cough, severe bulbar dysfunction, severe cardiac dysfunction or receiving muscular blocking agents or morphine infusions (Grade 1C).[20, 48] In fact, ICU setting allows intensive cardiovascular and respiratory monitoring and use of adjuvant therapy, including NIV, cough-assisted and suctioning devices.[16]

Finally, a very important pre-operative issue is to establish whether the benefit of surgery outweighs the anesthetic risk and *discuss risks and benefits* of surgical procedures with the patients and/or their family (Grade 1C).[13]

Preoperative considerations in specific NMDs

Myasthenia Gravis and Myasthenic syndromes

Drug therapy should be optimized (Grade 1C).[21, 49-56] If the patient is poorly controlled, a pre-operative course of plasmapheresis or i.v. immunoglobulins could be beneficial.[21, 49, 52, 56] However, there's little evidence that supports this strategy in order to reduce anesthesia complication. 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.[57, 58] When oral administration is limited, an equivalent dosage of intravenous neostigmin should be introduced and continued until the patient resumes oral therapy.[21, 52, 56]

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,[59] as excessive glycolytic oxidation may increase plasma lactate levels (Grade 1C).[60]

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.

An overview of the anesthetic strategies in NMDs is summarized in Table V.

Succinylcholine and halogenated agents

Four major categories of NMD_S should be considered to plan the safest anesthesia strategy (Table VI).

In motor neuron and peripheral nerve diseases the use of halogenated agents is permitted, whereas succinylcholine must be avoided (Grade 1C).[7, 13, 15, 16, 23, 26]

In patients with *neuromuscular junction disorders*, GA can be performed using halogenated agents (Grade 1C).[7, 13]

In myopathic patients the use of inhaled anesthetics and succinylcholine is classically considered at high risk for MH or acute rhabdomyolysis.[8] Although, only few muscle diseases carry significant risk of MH as some rare myopathies due to mutation of calcium channels (*e.g.*, ryanodine receptor), "central core myopathies", King–Denborough syndrome or other rarer conditions, all patients with muscle disease carry a risk of rhabdomyolysis.[7, 13, 11, 36, 61] Therefore, it is recommended to avoid the use of succinylcholine and halogenated agents in such patients (Grade 1C).[7, 8, 13, 15, 62, 63] However, in patients with mitochondrial myopathies, halogenated agents can be administered (Grade 2C).[8, 59, 60] Although some authors [8] agree that faced with a difficult venous access in a patient with myopathy a brief use of inhalation anesthesia is possible as long as the anesthesiologist is prepared to treat rhabdomyolysis, the committee agreed about the use of ketamine in these circumstances (Grade 2C). Although I.M. ketamine is used for adult patients, an oral or rectal route is preferred for pediatric patients to avoid unnecessary pain and stress to the child and their family.

Total intravenous anesthesia (TIVA)

If inhalation anesthesia has to be avoided, GA can be performed using TIVA (Grade 1C).[7, 37, 64] However, 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. Although the effectiveness of target controlled infusion (TCI) of propofol compared with manually controlled infusion remains controversial in adults and in children,[73] some authors reported that careful titration of propofol by TCI enables to evaluate the patient's sensitivity to propofol in subjects with NMDs.[65]

Moreover, despite its well-known limitation in pediatric patients [66, 67] the use of Bispectral Index Monitor (BIS) may prevent the occurrence of awareness and reduce the risk of drugs' overdose in patients with NMDs.[68, 69]

Non-depolarizing neuromuscular blocking agents (NMB)

In all patients with NMDs, non-depolarizing NMB may show prolonged duration of neu-

TABLE V.—*Overview of anesthetic strategies in neuromuscular diseases.*

Neuromuscular diseases	Regional anestesia	Volatile anesthetic	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 sensitivity against thiopental and propofol – Prevent myotonia avoiding AChE, hypothermia, electrical 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 propofol. 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.

romuscular blockade even when short-acting. Thus, most reports recommend avoidance of NMBs whenever possible (Grade 1C).[7, 23, 24, 70] However, 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),[20, 21, 37] and the effect of muscle relaxant should be antagonized (Grade 2C). Nevertheless, anticholinesterase drugs are not recommended because they may lead to hyperkalemia.[13] Therefore, 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.[71, 72]

Regional anesthesia

There are potential risks with regional anesthesia in patients with preexisting peripheral nervous system diseases. Upton and McComas [73] 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.

Table VI.—*Contraindications to the use of succinylcoline and halogenated agents in neuromuscular disorders.*

Neuromuscular disorders	Life-threatening complications related to the use of succinylcholine and/or halogenated agents	Succinylcholine	Halogenated agents
Motoneuron diseases and peripheral neuropathies	Hyperkalemic cardiac arrest secondary to denervation – triggered by succinylcholine – patients at risk: all subjects with motoneuron diseases and peripheral neuropathies	Contraindicated	May be used
Neuromuscular junction diseases		May be used; however, patients with MG show a relative resistance to succinylcholine, whereas patients with LES show an increased sensitivity to succinylcholine	May be used
Muscle diseases	Malignant hyperthermia – triggered by succinylcholine or halogenated agents – patients at risk: only subjects with diagnosis of RYR1 mutations and patients with central core disease, his variant core-rod myopathy and King–Denborough syndrome Rhabdomyolysis – triggered by succinylcholine or halogenated agents – patients at risk: all subjects with muscle diseases Myotonic contractures – precipitated by many factors like hypothermia, postoperative shivering, dyskalemia, mechanical and electrical stimulation or drugs (i.e., propranolol, succinylcholine and anticholinesterase agents) – patients at risk: all subjects with myotonic dystrophies	Contraindicated	Contraindicated in all muscle diseases except in mitochondrial myopathies

MG: myasthenia gravis; LES: Lambert-Eaton Syndrome.

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.[1, 7, 74] A significant reduction of the required volume of local anesthetic is possible when ultrasound or peripheral nerve stimulator are used for nerve identification. Moreover, the use of ultrasound appeared to reduce the incidence of hematoma formation following vascular puncture.[75] Therefore, regional anesthesia should be warranted whenever possible (Grade 1C), including patients with preexisting peripheral nervous system disorders (Grade 2C).[7, 22, 76, 77]

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).[78, 79] 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.[13] However, several cases have been reported in which epidural and spinal anesthesia were successfully used without haemodynamic instability.[77, 78, 80]

Myasthenia Gravis (MG) and Myasthenic Syndromes

Factors potentially enhancing neuromuscular blockade should be avoided (*e.g.* hypothermia, hypokalemia, hypophosphatemia and several drugs) (Grade 1C).[21, 57] As local anesthetic agents may block neuromuscular transmission,[49] subarachnoid and epidural anesthesia should be performed using reduced doses and preferably amid local anesthetics, such as bupivacaine and ropivacaine.[21, 81]

Excess of anticholinesterase drugs may produce flaccid muscle paralysis and pupil constriction (cholinergic crisis) in patients with MG. Many patients have a decreased requirement of these drugs in the first 48 hours. Thus, 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.[57] 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.[72]

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.[71]

Myotonic dystrophy

The anesthetic strategy of choice remains uncertain. Whenever possible, 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 patients with DM1 and DM2,[8, 48, 82, 83] but others consider safer to avoid them.[7, 15] Noteworthy, halogenated agents may induce postoperative shivering which can precipitate myotonia.[7] Moreover, there is an increased sensitivity of DM1 patients against thiopental and propofol.[64, 83] During anesthetic induction, 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.

In these patients respiratory insufficiency may be caused both by weakness or myotonic reactions. Many factors like hypothermia, postoperative shivering, dyskalemia, mechanical and electrical stimulation or drugs (*i.e.*, propranolol, succinylcholine and anticholinesterase agents) can precipitate myotonic contractures. 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.[7, 64] 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,[64] otherwise the treatment is mainly preventive, avoiding all triggering factors. Consequently, a protocol of safe surgical procedure should be adopted to prevent myotonia (Grade 1C). 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.[60, 84]

Careful cardiac monitoring is needed in all DM1 patients, for their high risk of arrhythmic events, which may cause sudden death at any age.[64, 85]

Finally, these patients have also a propensity to develop hyperglycemia, dysphagia and gastroesophageal reflux.[64] Maintaining the torso of the patient elevated in the postoperative period reduces the risks of aspiration.[64]

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.[13]

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, hemi-paresis, cortical blindness, ophthalmologic abnormalities, hearing loss), bulbar dysfunction with impaired swallowing, cardiac dysfunction, hepatic and renal disease, defect of insulin secretion.

It should be borne in mind that propofol has a mitochondrial depressant effect that can induce lactic acidosis.[8, 15] 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.[8, 15, 86] Nevertheless, it is noted that all these anesthetic agents have been used with success in patients with mitochondrial myopathies.[15, 59, 60] This suggests that there is no case for avoiding any particular anesthetic agents in these patients.[15, 59, 60] However, caution is required with all anesthetic agents.[60] In particular, it would be seen as pertinent to avoid the prolonged use of propofol for the maintenance of anesthesia.[60] Moreover, lactic acidosis should be prevented with control of excessive stress,[60, 84] maintaining normal serum glucose levels, adequate oxygen balance, stable cardiovascular function, and adequate gas exchange. Furthermore, the routine perioperative use of lactate-free i.v. fluids in all patients with mitochondrial disease undergoing GA is recommended.

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. In fact, 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. Such a condition may precipitate as a consequence of a decrease in systemic vascular resistance, preload, or both eventually induced by anesthetic agents, with an increased risk of intraoperative cardiac arrest.[87]

Postoperative management

Pain control

Adequate pain control is essential to prevent hypoventilation secondary to splinting after thoracic, upper abdominal and spine surgery (Grade 1C).[2, 5]

Intravenous opioids should be titrated to provide adequate analgesia and promote airway clearance minimizing respiratory suppression.[2, 5, 37, 88] This goal is best accomplished with preemptive analgesia and using multiple pharmacological agents.[89, 90] Oral clonidine administered preoperatively has been shown to reduce the requirement for postoperative analgesics.[91] 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.[92, 93]

Continuous infusion of opioids *via* epidural catheters can be used when appropriate to achieve pain control while minimizing respiratory side effects.[94, 95]

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.[16] 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.[96] These neural structures should be localized using ultrasound guidance or nerve stimulation techniques (Grade 1C).[75]

Neuropathic deep pain and dysesthetic burning pain that frequently occurs in Guil-

lain-Barre'Syndrome [97] may be treated using gabapentin.[98] In patients admitted to ICU not responding to treatment with gabapentin, remifentanil infusion can provide a satisfactory analgesia.[99]

In case of hypoventilation after opioid administration, adequate ventilation can be achieved by using NIV or by delaying extubation for 24 to 48 hours.[2] Moreover, MI-E can also be useful when pain prevents the patient from coughing spontaneously.

Respiratory management

Postoperative management should be determined by preoperative respiratory function and the type of surgery performed.[2, 5] Patients with normal cough clearance and relatively preserved muscle function are not at increased risk for postoperative complications.[5] On the other hand, patients with decreased respiratory muscle strength require close monitoring and aggressive respiratory management.[2, 5]

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 (Grade 1C).[2, 4, 29, 33, 100, 101]

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.[2, 5] 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 H_2O. These techniques should be used before and after extubation.[29] Assisted cough is obviously also recommended for patients already using MI-E and NIV preoperatively.

To maximize the chance of success, extubation should be delayed until respiratory secretions are well controlled and SpO_2 is normal or baseline in room air (Grade 2C).[102]

In patients requiring long-term mechanical ventilation (*e.g.*, patients with Guillain-Barre'Syndrome) respiratory support must be continued in the postoperative period (Grade 1C).[5, 103]

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.[102] To facilitate appropriate oxygen use, CO_2 levels should be monitored (Grade 2C).[2, 5]

Conclusions

Patients with NMDs are at high risk of intraoperative and postoperative complications. An intensive, proactive, multidisciplinary approach should be instituted before, during and after any surgical procedure requiring GA or sedation. Thus, surgery in this patient population should be performed in a fully equipped hospital with extensive experience in NMDs management.

Key messages

— All NMDs patients with limited respiratory reserve should be trained to use NIV and manual or mechanically assisted cough techniques prior to surgery and assisted with these devices during sedation and in the postoperative period (Grade 1C).

— Regional anesthesia should be adopted whenever possible (Grade 1C), including patients with preexisting peripheral nervous system disorders (Grade 2C).

— Succinylcholine must be avoided in all NMDs except in patients with neuromuscular junction diseases (Grade 1C).

— Halogenated agents must be avoided in all patients with muscle disease (Grade 1C), except in patients with mitochondrial myopathies (Grade 2C).

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