Review

Perioperative risks in neuromuscular diseases: An update

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Abstract

Patients with neuromuscular diseases are at a high risk of peri-operative complications. Recent advances in the management of these disorders have increased the survival rates and the need for surgical procedures related or non-related to the primary disorder. Cardiac and respiratory failure are by far the commonest complications in addition to rhabdomyolysis, malignant hyperthermia, myotonic contractures and peri-operative drug induced complications. Meticulous pre-operative assessment, optimization and a high index of suspicion for complications reduce the risks. Regional anesthesia is generally safer. If general anesthesia is required special precautions should be taken. These may vary form disease to disease and thus a multi-disciplinary approach involving the parent surgical team, neurology team, medical team, intensivist and anesthetist is of paramount importance. In this brief update the perioperative assessment and management of the common complications have been discussed along with a brief insight into the anesthetic drugs that may potentiate complications. A very brief description of the common neuromuscular disorders and respective anesthetic considerations has also been mentioned.

Index words: neuromuscular disorders, peri-operative risks, complications, anesthesia

Introduction

Neuromuscular disorders (a heterogenous group of diseases that affect the skeletal muscles), not very uncommon in the current clinical settings, comprise of hereditary and acquired disorders. Recent advances in the management of neuromuscular disorders have resulted in better survival rates and the need for surgical procedures related or non-related to neuromuscular disorders. This poses a concern for the anesthetists, intensivists, the parent medical and surgical team and the neurology team. Understanding the pathophysiology of each condition facilitates peri-operative planning. Precise preoperative diagnosis prior to anesthesia is ideal though not always feasible. Thus, preplanned strategies should be in place should any complication arise.

Hereditary neuromuscular disorders may be pre-junctional (peripheral neuropathies such as hereditary sensory motor neuropathies, Fredrich's ataxia), post-junctional (dystrophias, myotonias, familial periodic paralysis) and metabolic and mitochondrial (metabolic myopathies, mitochondrial myopathies) disorders. Acquired neuromuscular disorders include pre-junctional disorders (motor neuron disease, multiple sclerosis, Guillain-Barre syndrome, peripheral neuropathies), neuromuscular junctional disorders (myasthenia gravis, Eaton-Lambert syndrome) and post-junctional disorders (critical illness polyneuropathy, critical illness myopathy). Patients with neuromuscular diseases have altered vital functions and an increased risk of morbidity and mortality associated with surgical procedures requiring general anesthesia or sedation. Some anesthetic agents trigger life threatening reactions like malignant hyperthermia, rhabdomyolysis or hyperkalemic cardiac arrest secondary to denervation.

Table 1 summarizes the common neuromuscular diseases encountered in routine clinical practice and some important anesthetic considerations.

Pre-operative assessment and management

A detailed neurological diagnosis is essential to confirm the diagnosis and identify the level of progression when feasible and assess risk during surgery and anesthesia[1]. Patients presenting without a definite diagnosis, particularly with isolated elevated creatinine kinase with or without minor signs should be considered as high risk subjects[2]. Ideally there should be a full discussion with the patient and the family regarding the potential risks and complications, preassessment of functional status and associated comorbid conditions, anesthetic strategies and post-operative care plan. High incidence of cardiac and respiratory complications warrant a through pre-operative assessment of these systems. Further the severity of the cardio-respiratory function does not correlate with the progression of the neuromuscular disorder.

Respiratory assessment: Respiratory involvement varies with each disease. Reduced respiratory muscle strength results in restrictive pulmonary impairment with a progressive decrease in forced vital capacity (FVC), ineffective alveolar ventilation leading to nocturnal hypercapnia and later to diurnal hypercapnia. There is

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inadequate clearance of airway secretions, hypoventilation and impaired cough which predispose atelectasis and respiratory failure. Aspiration and micro aspiration are common with bulbar dysfunction. Respiratory status may be further impaired by sleep apnea, nutritional problems, gastro-esophageal reflux or progressive scoliosis. Anesthetic agents decrease respiratory muscle strength, exacerbate hypoventilation, airway secretion retention, aspiration, obstructive and central apneas. These lead to nosocomial infections, prolonged intubation, tracheostomy and eventually death. Thus, all patients should have an extensive preoperative pulmonary assessment and well planned perioperative and postoperative management plan[3,4,5].

Table 1. Common neuromuscular disorders and anesthetic considerations

Neuromuscular disorder	*Anesthetic considerations*
Hereditary Sensory Motor Neuropathy	• Avoid depolarizing neuromuscular blocking agents • Effects of non-depolarizing neuromuscular blocking agents may be prolonged • Anesthesia can be maintained by intravenous or volatile agents • Respiratory compromise may lead to post-operative ventilation • Neurological deficit should be noted before regional anesthesia
Fredrich's ataxia	• Respiratory failure due to diaphragmatic involvement • Depolarizing neuromuscular blocking agents should be avoided • Risk of aspiration due to upper motor neuron involvement • Negatively inotropic drugs should be used carefully due to myocardial involvement
Duchenne's muscular dystrophy / Becker's muscular dystrophy	• Post-operative respiratory insufficiency • Post-operative cardiac dysfunction related to cardiomyopathies or arrythmias • Post-operative ventilatory support and cardiac monitoring • Appropriate pre-operative assessment • Increased blood loss due to smooth muscle and platelet dysfunction • Hypotensive anesthesia recommended to avoid large blood volume loss • Hypovolemia avoided due to relatively fixed cardiac output secondary to non-compliant ventricles • Volume status should be monitored invasively in potential cases for hypovolemia • Volatile anesthesia and depolarizing neuromuscular blocking agents are avoided in female carriers • Depolarizing neuromuscular agents must be avoided • Non-depolarizing muscular agents sparingly used • Avoid inhalation agents due to rhabdomyolysis • Extreme caution with total intravenous anesthesia and a clean anesthetic machine is advisable • If induction using volatile anesthesia is indicated, then inhalation agents should be discontinued as soon as possible with conversion to total intravenous anesthesia and a clean anesthetic machine

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Neuromuscular disorder	*Anesthetic considerations*
Myotonic dystrophy	• Avoid factors that may precipitate myotonia eg. Hypothermia, shivering, mechanical and electrical stimulation • Increased sensitivity to sedatives and analgesics • Depolarizing neuromuscular blocking agents not recommended (may induce generalized muscular contractures) • Anticholinesterases may precipitate contractures due to increased sensitivity to acetylcholine • Peri-operative blood glucose monitoring due to impaired glucose metabolism • Bulbar weakness predisposes to aspiration • Cardiac conduction defects may require pacing
Myotonia congenita	• Avoid depolarizing neuromuscular blocking agents (may induce intractable myotonias) • Avoid cold environments, post-operative shivering, excessive physical manipulation • Non-depolarizing neuromuscular blocking agents / peripheral nerve blocks will not relax contractions • Sodium channel blockers may be useful in breaking the contractures
Hyperkalemic periodic paralysis	• Loop diuretics to aid pre-operative potassium depletion • Avoid drugs causing potassium release from the cells – depolarizing neuromuscular blocking agents, potassium containing fluids • Continuous ECG monitoring • Calcium for emergency treatment of hyperkalemic weakness • Minimize fasting • Infuse glucose containing fuids during fasting • Avoid hypothermia • May remain paralyzed for hours after surgery • Use of volatile agents and non-depolarizing neuromuscular blocking agents is thought to be safe
Hypokalemic periodic paralysis	• Potential link with malignant hyperthermia • Volatile agents should be avoided • Depolarizing muscular agents should not be given • Avoid drugs that cause serum potassium shifts including salt and glucose loads • Maintain normothermia • Ensure serum potassium is within normal range • Avoid anxiety (can precipitate weakness) • May need post-operative ventilation should a peri-operative attack occur • Cardiac arrythmias

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Neuromuscular disorder	*Anesthetic considerations*
Metabolic myopathies	• Metabolic monitoring during perioperative phase • Adequate hydration with forced diuresis to avoid myoglobinuria • Glucose and amino acid infusion to aid muscle metabolism • Prevent hypothermia • Prevent shivering
Mitochondrial myopathies	• Temporary pacing in the event of total atrio-ventricular block • Control blood glucose • Avoid prolonged fasting • Infuse sodium lactate • Anticipate post-operative respiratory failure • Aspiration due to impaired swallowing • Low dose volatile inhalation anesthetics and ketamine recommended • Local anesthetics and propofol should be avoided or given in reduced concentration due to depressant effect on mitochondria
Motor neuron disease	• Depolarizing neuromuscular blocking agents should be avoided • Non-depolarizing neuromuscular blocking agents may be used in reduced doses due to increased sensitivity • Respiratory complications including risk of post-operative ventilation, weaning difficulties, infection and atelectasis common
Multiple sclerosis	• Local anesthetics may exacerbate symptoms due to increased sensitivity of demyelinated axons to local anesthetic toxicity • Non-depolarizing neuromuscular blocking agents may be used in normal doses • Depolarizing neuromuscular agents should be used with caution or best avoided if the patient is debilitated • Maintain normothermia as symptoms deteriorate with an increase in temperature (demyelinated axons are more sensitive to heat)
Guillain Barre' syndrome	• Intubation and ventilation most likely required • Invasive monitoring due to risk of autonomic instability • Depolarizing neuromuscular blocking agents avoided (should be avoided even after prolonged period of recovery due to the risk of hyperkalemic cardiac arrest • Increased sensitivity to non-depolarizing neuromuscular blocking agents • Avoid post-operative opioids • Can use epidural anesthesia
Diabetic peripheral neuropathy	• Invasive monitoring due to autonomic instability • Anticipate and manage gastroparesis at induction and post-operative period due to autonomic instability • Maintain normothermia due to increased likelihood of hypothermia

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Neuromuscular disorder	*Anesthetic considerations*
Myasthenia gravis	• Relative resistance to depolarizing neuromuscular blocking agents (requires only 10% of normal dose) • Avoid cholinesterase inhibitors (prolong the duration of depolarizing neuromuscular blocking agents and also may precipitate a cholinergic crisis) • Avoid drugs that interfere with neuromuscular transmission • Post-operative ventilation may be needed
Eaton-Lambert Syndrome	• Sensitive to depolarizing neuromuscular blocking agents and non-depolarizing neuromuscular blocking agents • Anticholinesterases can be given • Autonomic dysfunction due to relative lack of acetylcholine • May need post-operative ventilation
Critical illness polyneuropathy /myopathy	• Prevention as there is no specific treatment • Avoid prolonged infusions of non-depolarizing neuromuscular blocking agents specially when high dose steroids are used • Avoid depolarizing neuromuscular blocking agents to prevent cardiac arrest

Pulmonary assessment should include an accurate medical history and physical examination, chest X ray, evaluation for sleep disordered breathing, measurement of respiratory functions and cough effectiveness (forced vital capacity, maximum inspiratory pressure, maximum expiratory pressure, peak cough flow, diurnal pulse oximetry). Patient's respiratory status should be optimized before surgery. Patients with indication for non-invasive ventilation and manual or mechanically assisted cough techniques should be trained in the use of assistive devices pre-operatively[6].

Cardiac assessment: Neuromuscular diseases are associated with cardiac dysfunction, cardiomyopathies and / or abnormalities of the conduction system. With the limited ability to increase cardiac output in response to stress and unrecognized or delayed recognition of the clinical manifestations of heart failure[6,7] further confounded by the negative inotropic effects of volatile and intravenous anesthetic agents, positive pressure ventilation, hypoxemia and acute anemia[8] place the patient at high risk for perioperative cardiac side effects. Sensitization of cardiac muscles to catecholamines and the inhibitory effects in voltage-gated potassium channels induce arrhythmias specially when using volatile anesthetics[1]. Pulmonary hypertension secondary to nocturnal hypoxia is a known complication.

All patients require a comprehensive preoperative cardiac assessment and optimization of cardiac therapies. All patients should have an electrocardiogram and echocardiogram, particularly if not done in the previous 12 months[7,9]. All patients with signs and symptoms of arrythmias should have a Holter monitoring[6,9] and a long QT which suggests Andersen syndrome should be excluded in patients with periodic paralysis as it predisposes them to ventricular arrythmias. Patients with a high degree AV block may need cardiac pacemaker before general anesthesia. Those with severe cardiac dysfunction will benefit from invasive arterial pressure monitoring during general anesthesia and in the post-operative period[10]. Preoperative cardiac evaluation is advocated in patients without primary myocardial dysfunction only if pulmonary hypertension is suspected.

In addition to comprehensive cardiac and pulmonary assessment a general assessment and optimization of the patient's medical status should be considered with respect to reducing perioperative complications and enhancing recovery. Poor nutritional balance leads to poor wound healing, inability to clear secretions and maintain adequate ventilation and associated respiratory complications. Thus, a nutritionist assessment and nutritional optimization is mandated[3,11]. Increased sensitivity to premedication drugs could result in sleep apnea and hypoventilation[12]. Patients on chronic treat-

ment with steroids may have suppression of the hypothalamic-pituitary-adrenal axis and susceptible to develop adrenal insufficiency during a phase of stress and should be assessed and managed with expert opinion. Jaw ankylosis, atrophy of the masseter and other muscles of mastication, macroglossia and limited mobility of the cervical spine[6,11,12] categorize the patient as for management as difficult airway management. Ultrasound assisted peripheral cannulation may be needed for difficult intravenous access. With the patient being at a high risk of perioperative and post-operative complications post-operative ICU care should be arranged.

Peri-operative management

The most important issues in peri-operative and intra-operative management are the maintenance of the vital parameters, choosing the appropriate anesthetic agent and having a high index of suspicion to identify the possible rare complications. Patients should be meticulously monitored throughout the surgery with ECG, oxygen saturation, capnography and other standard monitoring as for any surgery. Invasive arterial blood pressure monitoring is recommended in potentially unstable patients.

Patients with neuromuscular disease are vulnerable to both hypothermia and hyperthermia. Reduced heat production and peripheral vasodilation of general and regional anesthesia predispose hypothermia. Normothermia should be ensured before induction and maintained using warm fluids and air warmers if needed. Exacerbation of myotonia, increased sensitivity to non-depolarizing neuromuscular blocking agents, rhabdomyolysis, bleeding and arrythmias are some of the life-threatening complications of hypothermia. Hyperthermia indicated by unexplained tachycardia, increased end tidal CO_2 concentration should be detected and treated aggressively. Patients with myotonias and muscular dystrophies should alert the team of the possibility of concomitant malignant hyperthermia.

Regional anesthesia is of advantage in patients with cardiac and respiratory impairment. However, they are best avoided in patients with rapidly progressive neurological deterioration in order to distinguish regional blockade from disease progression. Sympathetic blockade may aggravate autonomic dysfunction and necessitates the use of invasive monitoring and careful titration of hypotensive agents.

Use of volatile general anesthetic agents are controversial due to the association of malignant hyperthermia with some neuromuscular disorders such as Duchenne muscular dystrophy. Total intravenous anesthesia with a clean anesthetic machine are used to avoid rhabdomyolysis. Volatile agents are avoided as they cause cardiovascular decompensation due to cardiodepressive and arrhythmogenic properties. Total intravenous anesthetics are beneficial as they are short acting and relatively easy to control, however need caution due to the risk of autonomic dysfunction and cardiovascular collapse.

Neuromuscular blockade can be achieved by using depolarizing and non-depolarizing blocking agents but have to be used with caution. Depolarizing neuromuscular agents such as succinylcholine are not recommended as succinylcholine activates nicotinic acetylcholine receptors leading to an influx of cations into the sarcolemma, resulting in immobility of denervated muscles for prolonged periods. Further they increase the number of acetyl choline receptors throughout the muscle membrane and promote the development of fetal gamma isoform of the nicotinic acetylcholine receptor subunits. Acetylcholine activates both receptor groups leading to membrane depolarization and potentially massive potassium efflux which in turn causes fatal hyperkalemia, muscle fiber swelling and rhabdomyolysis. Fasciculations caused by succinylcholine may cause temporomandibular muscle spasm and may prevent intubation and ventilation in myotonias[1,13,14]. Interestingly myasthenia gravis patients are relatively resistant to succinylcholine and required dose may be increased up to two folds. Judicious use of total intravenous induction helps avoid non-depolarizing agents, since patients who are sensitive may develop respiratory weakness and difficult weaning, sputum retention and dysphagia. If a non-depolarizing neuromuscular agent is absolutely needed a 10 to 20% dose reduction is recommended with mivacurium and atracurium being the preferred agents due to their degradation process. Anticholinesterases cause hyperkalemia and are not recommended in muscle dystrophies.

Post-operative management

Patients with neuromuscular diseases are not suitable for day case surgery. They required planned elective surgery with planned admission and post-operative admission to high dependency or intensive care unit is mandatory. Institution of early and appropriate physiotherapy, positive pressure circuits and appropriate analgesics reduce post-operative complications. Post-operative pain and respiratory management play an important role in the outcome.

Pain management

Optimal pain control is of significant importance in patients with neuromuscular diseases and is achieved with preemptive analgesia and using multiple pharmacological agents. Hypoventilation secondary to splinting after thoracic, upper abdominal and spinal surgery can be prevented with adequate pain control[6]. Providing

adequate analgesia by titrating intravenous opioids helps airway clearance and minimizing respiratory suppression[6,11,12]. Post-operative analgesic requirements can be reduced by preoperative administration of clonidine or the use of intravenous paracetamol alone or in combination with non-steroidal anti-inflammatory agents[15,16]. Optimal analgesia with minimal respiratory side effects can be achieved by continuous infusion of opioids via epidural catheter when appropriate[17]. Wound infiltration with local anesthetics and continuous infusion of local anesthetics via a peripheral nerve block are safer alternatives. Peripheral nerve blocks provide comparable analgesia with less side effects compared with epidural[18]. Neuropathic deep pain and dysesthetic burning pain can be treated with gabapentin.

Respiratory management

Optimal management of post-operative respiratory management plays a crucial part in the recovery of the patient and depends on the pre-operative respiratory function and the type of surgery[6,11]. Those with normal cough clearance and relatively preserved muscle function are not at increased risk, while those with decreased respiratory function require close monitoring and aggressive management. Combination of non-invasive ventilation with mechanical insufflation and exsufflation after extubation of high risk patients reduce the need for reintubation or tracheostomy and shortens the ICU stay[11,19,20]. In patients with baseline FVC < 50% of predicted should be considered for extubation directly to non-invasive ventilation[6,11]. Subjects with preoperative peak cough flow (PCF) < 270 l/min or maximum expiratory pressure (MEP) < 60 cm H_2O should be supported with assist cough techniques[21].

Extubation must be delayed until respiratory secretions are well controlled and SpO_2 normal or baseline at room air[22]. Respiratory support must be continued in the post-operative period in patients requiring long term mechanical ventilation. In addition to correcting hypoxia, treating the underlying causes such as hypercapnia, mucus plugging, and atelectasis is important. CO_2 levels should be monitored to facilitate appropriate oxygen use.

Post-operative complications

Common post-operative complications include rhabdomyolysis, autonomic dysfunction, myotonias, cardiac and respiratory complications and malignant hyperthermia.

Rhabdomyolysis: Depolarizing neuromuscular blocking agents cause massive changes in ion distribution with muscle contraction, swelling and damage leading to rhabdomyolysis. Volatile agents may also cause malignant hyperthermia. Metabolic acidosis, hyperkalemia, myoglobinuria, creatinine kinase >10,000 U/L are suggestive of rhabdomyolysis and management includes cessation of the potential causative agent, correction of life-threatening hyperkalemia and maintaining a urine output of 1ml/kg/hour. Urine may be alkalinized using sodium bicarbonate. Dantrolene is used in the management of hyperthermia.

Autonomic dysfunction: Common in neuromuscular diseases may cause severe hypotension on induction and after regional anesthesia. It also causes gastric dysmotility leading to regurgitation and aspiration specially during general anesthesia. Sympathomimetic drugs should be available, and doses may need to be reduced due to increased sensitivity of alpha and beta receptors.

Myotonia: Myotonic contractures can occur in dystrophic and non-dystrophic myotonic disorders. Repeated action potentials lead to a permanent sodium influx or chloride efflux across the muscle membrane making it hyperexcitable. Drugs such as succinylcholine, anticholinesterases and opioids and environmental factors including alteration in temperature, acidosis and shivering trigger a contraction. If a myotonia is triggered they are not classically responsive to neuromuscular block, regional or peripheral nerve blocks. Management includes correction of environmental and physiological conditions and removal of the offending drug when possible. Drugs of choice in the management include drugs which block sodium channels such as local anesthetics and antiarrhythmic agents.

Cardiac complications: Cardiomyopathies and conduction abnormalities increase the morbidity and mortality. Perioperative catecholamine release precipitate arrythmias and potentiate cardiac failure. Patients should have acess to invasive monitoring, inotropic drugs and high level post-operative care.

Respiratory failure: This is the commonest cause of death in patients with neuromuscular diseases and also results in repeated aspiration (bulbar weakness), poor pharyngeal and respiratory muscle tone, obstructive sleep apnea and progressive spinal deformities leading to restrictive lung disease. Management includes extubation as early as possible to prevent further weakening of respiratory muscles. However, this needs to be weighed against the risk of atelectasis, aspiration, infection and respiratory failure.

Malignant hyperthermia: There is an increased risk of malignant hyperthermia during anesthesia. This may occur as a true malignant hyperthermia or a contracture related rhabdomyolysis and acidosis. Management has been discussed under rhabdomyolysis.

Conclusion

Patients with neuromuscular disease are at a high risk of intraoperative and postoperative complications and thus require a multidisciplinary team approach to be in place in the perioperative period. Surgery should be performed electively and only in hospitals which are fully equipped and with experience in managing patients with neuromuscular disorders. In emergency situations the essential lifesaving procedures should be performed and patient should be stabilized and transferred to a fully equipped hospital.

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