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REVIEW ARTICLE

Perioperative management of the patient with Myasthenia gravis

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Abstract

Myasthenia gravis is an autoimmune disease in which autoantibodies interact postsynaptic nicotinic acetylcholine at the neuromuscular junction which decreases the capacity of the terminal plate to transmit the nerve signal. For the anesthesiologist may be difficult extubation at the end of the procedure, especially if interference drugs are used at the neuromuscular junction. This review addresses the steps to be followed in perioperative management with flowcharts.

Key words: *Myasthenia gravis. Perioperative management. Anesthesiology.*

Introduction

Myasthenia gravis (MG) comes etymologically from Latin and Greek and means "severe muscle weakness." Autoantibodies interact against postsynaptic acetylcholine receptors (AChR) in the neuromuscular nicotinic junction[1] and decrease the ability of the endplate to transmit the nerve signal in this autoimmune disease. In the first place, as a response to this stimulus, depolarization occurs with the release of acetylcholine. The number of activated postsynaptic receptors may be insufficient to trigger a potential for muscle action. Subsequently, with repeated stimulation, the release of acetylcholine is correlated clinically with fatigue and muscle weakness[2].

AChR antibodies reduce the number of functional receptors, which decreases acetylcholine binding, preventing muscle contraction. The rate of degradation of the receptors is also increased, and consequently, damage to the neuromuscular junction occurs. Thus, in patients with MG, the density of AChR is reduced so that the total number of receptors will be 30% less than the normal[1].

The weakness is accentuated with exercise and decreases with rest, in 15% of patients. The disease occurs in the ocular muscles presenting diplopia and ptosis. However, in the remaining 85%, the disease is a generalized producing weakness in the eye, facial muscles, and appendicular apparatus. The respiratory muscles are usually mildly affected, but even then, the patient may require artificial ventilation. The anatomical distribution of the weakness and the response to pharmacological treatment allows to classify MG[1].

Although it is widely accepted that MG is a condition caused by antibodies, the origin remains uncertain. However, the thymus gland becomes a possible generator of the autoimmune process[3].

In 75% of patients with MG, the thymus gland is abnormal (85% with hyperplasia and 15% with thymoma)[1].

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These patients are usually a challenge for anesthesiologists because of the risk of post-operative respiratory failure[4].

Epidemiology

The prevalence and incidence of MG have increased, showing an incidence rate of 5.3 persons per million and a prevalence of 77.7 persons per million. This phenomenon to detect more MG cases could be attributed to better diagnosis and treatment[4].

MG affects a small part of the population, especially young women between 20 and 30 years of age and men over 60 years of age[4].

Diagnosis

The diagnosis of MG depends on the physical examination and clinical history conducted in addition to pharmacological tests, electromyography, and antiretroviral anti-nicotinic AChR (anti-nAChR) arrest[5].

One test used for diagnosis of the disease is the edrophonium test which works as an inhibitor of the cholinesterase. And this is positive when an improvement in strength is seen after the administration of 10 mg of the drug, demonstrated by a remarkable increase in muscular strength after 30 seconds and sustained for approximately 5 min if it is combined with an antibody detection of anti-nAChR or tyrosine-kinase in an specific muscle, and in adidition with clinical symptomps.

The anti-nAChR antibodies are detected in 80-85% of patients with MG and are pathognomonic of diseases. In the most part of patients with positive antibodies, thymus is affected due to a thymoma or an abnormal tumour in the gland[4].

Although historically the edrophonium test is used as secondary evidence for the diagnosis of MG, a negative result does not exclude the diagnosis, for which a record of the muscular action potentials is required[1]. Repetitive stimulation of the motor nerve results in a progressive decrease of more than 10% muscular electrical response changes[1].

The presence of choline antibodies in the serum, detected by radioimmunoassay, also establishes the diagnosis of MG. However, not all patients with mild symptoms can be detected[2].

Classification

There are clinical manifestations that allow to classify myasthenia as acute and chronic as in pediatric and adult[6].

Transient neonatal myasthenia occurs in 10-15% of deliveries of mothers with common MG and is due to antibodies against AChR produced by the mother that manage to pass the placental barrier. It is a transitory process that can be minimal or very serious, threaten the life of the newborn and last up to 6 weeks (the majority of cases past between 7 and 21 days)[6].

Although juvenile myasthenia has some clinical characteristics that distinguish it, if it does not differ greatly from that of adults, if the onset is early, we must rule out transient forms in the neonatal period and congenital myasthenic syndromes in the 1st year of life. Regarding the complementary tests that support the diagnosis, only acetylcholine anti-receptor antibodies (AChR) are found in 30-60% of cases. The performance of an electrophysiological study with repetitive stimulation or an isolated fiber EMG can present technical difficulties in children under 12 years[6,7].

The clinical forms of the adult are very well characterized, as explained in the classification of Osserman-Genkis and Merggioli (Tables 1 and 2).

About 10-20% of patients with MG do not have antibodies detected by radioimmunoassay techniques that are called seronegative. Although there are cases in which they present generalized symptoms, the majority of these patients are patients with mild and localized muscle weakness. It has been proposed that these patients probably have antibodies that are not detected by radioimmunoassay techniques since the transfer of serum from seronegative patients causes the disease in animal models. This shows that the autoimmune theory of seronegative myasthenia is different from seropositive myasthenia presenting improvement with immunotherapy (plasmapheresis, immunosuppressive drugs, and thymectomy)[1].

It is important to mention that up 20% of MG can be seronegative to nAChR but seropositive to MuSK. Patients with Musk-positive antibodies often develop prominent oculobulbar muscle weakness, whereas nAChR-positive patients usually develop generalized muscle weakness[1]. One of the most practical distinctions among them is the difference in response to treatment[4]. Patients with Musk-positive antibodies often develop prominent oculobulbar muscle weakness, whereas nAChR-positive patients usually develop generalized muscle weakness[1]. One of the most practical distinctions among them is the difference in response to treatment[4].

In patients with positive Musk antibodies, the cholinesterase inhibitors have no effect or can even worsen the symptoms. In these cases, thymectomy is not

Table 1. Osserman classification. Modified from Osserman K. Studies of myasthenia gravis: a reference for health-care professionals, in myasthenia gravis foundation of America 200

Stage	0	Without clinical data.
Stage	I	Muscular weakness in eye muscles.
Stage	II IIA IIB	Weakness that affects another muscle group that is not ocular. Affect extremities, axial muscles, or both. It affects oropharyngeal or respiratory muscles.
Stage	III IIIA IIIB	Moderate weakness affecting another muscle group other than the eye. It affects extremities, axial muscles, or both. It affects oropharyngeal or respiratory muscles.
Stage	IV IVA IVB	Severe weakness affecting another muscle group, not the eye. It affects extremities, axial muscles, or both. It affects oropharyngeal or respiratory muscles.
Stage	V	Intubated patient with or without mechanical ventilation support and does not include the patient in postoperative management in a patient with MG.

Table 2. Known subtypes of myasthenia gravis. Modified from Merggioli M. Autoimmune myasthenia gravis emerging clinical and heterogeneity, lancet neurol 2009;8:475-490

Type	Age of onset (years)	Clinical history	Antibodies	Comments
Early onset	< 40	Hyperplasia	Acetylcholine R	Relation men: women 1:3 Predominant in masculine sex.
Late-onset	> 40	Normal o atrphic.	Acetylcholine R, titin, ryanodine receptor	Greater severity than early start
Asociada atimoma	Usually 40-60	Neoplasia	Acetylcholine R, titin, ryanodine receptor	Without sex predominance, it may be associated with pareneoplastic syndromes.
MUSK	< 40 (la mayoría de los casos)	Normal	MuSK	It predominates in the female sex. Oropharyngeal, facial and respiratory selectivity in some cases.
Seronegative	Variables	Hiperplasia (some cases)	Acetylcholine R low affinity in 66%	Clinical Heterogeneity.
Ocular	Adults in USA and Europe, children in Asia	Unknown	Acetylcholine R in 50%	Predominant type in asian population.

indicated and patients may be relatively resistant to conventional immunotherapy including immunoglobulins[4].

It is important in the context of anesthesiology that differences in sensitivity to nondepolarizing neuromuscular blockers have not been demonstrated among seropositive and seronegative[4].

Treatment

Medical treatment options include specific immunosuppressive therapy with azathioprine, methotrexate, cyclosporine, immunoglobulins, plasmapheresis, and acetylcholinesterase inhibitors and as for surgical treatment, thymectomy[4].

Weakness may improve in the short-term through plasma exchange and immunoglobulins[2].

The objective of treatment with anticholinesterase therapy is to improve neuromuscular transmission by delaying the degradation of acetylcholine in the neuromuscular plate[2]. Pyridostigmine is the most commonly used drug within this classification and begins to act within the first 30 min, has a peak effect of 2 h and a half-life of approximately 4 h[2]. It is often very effective at the beginning of treatment, but its effects may decrease over time, and most of the patients require immunosuppressive therapy[1].

Corticosteroids are the mainstay of treatment. Prednisolone is initially administered at 20 mg/day, gradually

increasing to 60 mg/day and many patients show a worsening in weakness during the first 2 weeks of treatment[2]. Once the MG is controlled, the dose is gradually decreased to the lowest effective rate on alternate days. Azathioprine 1-2 mg/kg daily is often administered in combination with prednisolone to allow a reduction in the dose of corticosteroid[1].

Cyclosporin 5 mg/kg/day has been used as an alternative to prednisolone, but its high cost and nephrotoxicity limit its use[1].

Thymectomy is associated with an improvement in prognosis[4] and is indicated for the majority of patients with MG younger than 60 years and/or those with thymoma[1].

In patients with thymic hyperplasia, the objective is to induce remission or at least produce sufficient improvement. The treatment is based on immunosuppressive drugs, although the desired effect may take several years to appear[1].

Plasmapheresis is reserved for producing short-term remission in patients with significant weakness related to myasthenia, myasthenic crisis, or those who need to be improved before thymectomy[1]. The effect is correlated with a reduction of anti-AChR antibodies and an improvement in muscle strength is obtained within a few days, although it is usually of short duration[1,2].

If the patient is in a myasthenic crisis and undergoes emergency surgery, the patient should be optimized with plasmapheresis[4]. This acts by removing antibodies against acetylcholine reducing plasma levels after repeated treatment and correlating it with clinical improvement. It can also be effective even when the antibodies have not been demonstrated suggesting that common studies do not always detect pathogenic antibodies. The improvement is moderate to marked in almost all patients, but almost always they relapse after 4-8 weeks due to the reaccumulation of pathological antibodies[6].

During the procedure, there is a consensus to maintain prior medical therapy concomitantly with plasmapheresis. Either with anticholinesterase or immunosuppressants adjusting the doses, except in the face of a cholinergic crisis or doubt regarding the crisis type of the patient. In such a case, it is suggested to discontinue the anticholinesterase. The efficacy of FP in MG is widely accepted, although it has never been subjected to controlled studies[6].

Although there is no agreement on the standardization of spare volume, the benefit of plasmapheresis would not be achieved with < 50 ml/kg. It is common to remove 2-3 L of plasma daily or 3 times a week until the patient improves (usually 3-5 refills). The beneficial effect begins at 48 h and remains between 4 and 6 weeks[8].

Complications of plasmapheresis include hypotension, bradycardia, electrolyte imbalance, hemolysis, infection, and vascular access complications (e.g., pneumothorax during central catheter placement)[8-10].

As for the administration of immunoglobulin, the indications are similar to those used for plasmapheresis[1]. The improvement occurs within the 1st day and can be maintained for months. The complications include headaches and in rare cases, renal failure[1].

Avoid drugs that exacerbate MG. Some medications that can worsen the weakness are antibacterial drugs of the polymyxin group by causing a blockage of ion channels and AChR, aminoglycoside antibiotics decreasing the release of ACh and sensitivity postsynaptic AChR, procainamide, quinine, and beta-adrenergic blockers exacerbating weakness[1].

The myasthenic patient is at risk of developing two types of crisis: the myasthenic and the cholinergic[4].

The myasthenic crisis is an exacerbation of the disease, which can be caused by various factors including respiratory infections, emotional stress, and surgeries[4]. They are characterized by exacerbation of symptoms with increased muscle weakness and respiratory deficiency[4]. These crises usually develop during the first 2 years of the disease. The most important predictors of death are age, time of recognition of the crisis, and the need for endotracheal intubation. This type of crisis requires additional doses of cholinesterase inhibitors. In case the patient does not improve, intravenous immunoglobulins, plasmapheresis, and/or endotracheal intubation are necessary.

The cholinergic crisis occurs when the patient is overdosed with cholinesterase inhibitors and may show symptoms such as excessive salivation, sweating, abdominal cramps, urinary urgency, bradycardia, muscle fasciculations, or muscle weakness[4]. Treatment includes endotracheal intubation, atropine, and the suspension of cholinesterase inhibitors until the cessation of the crisis[4].

The two types of crisis (cholinergic crisis or myasthenic crisis) can be difficult to distinguish. It is useful to administer a single dose of edrophonium because the symptoms will improve if the patient has a myasthenic crisis, but if it is a cholinergic crisis, the patient may not show improvement or even worsen[4].

Pre-operative considerations

Some doctors have tried to develop scoring systems to predict the risk of myasthenic crisis after a surgical event[4,11].

In 1980 Leventhal et al. found that patients who have MG before the age of 6 years, presence of a respiratory problem before the disease or who are with lung disease at the time of surgery as risk factors for the myasthenic crisis[4,12].

Other investigators found that among the risk factors for mechanical ventilation after surgery were the previous use of cholinesterase inhibitors, severe bulbar symptoms, respiratory crisis, and/or MG-related cardiorespiratory disease[4,13].

A study conducted in Japan in 2004 showed that the risk factors for myasthenic crisis after surgery were the presence of antibodies to the AChR of pre-operative serum level > 100 nmol/l and/or transoperative loss of 1 L or more of blood in addition to the bulbar symptoms and a history of the previous myasthenic crisis[4].

Therefore, previous respiratory complications and symptoms are more important risk factors for the use of mechanical ventilation after surgery[4].

The ability of the patient to protect and maintain the airway permeable in the post-operative period can be compromised if the patient had a respiratory implication such as decreased ability to read and manage secretions. Ventilatory muscle strength can be quantified by pulmonary function tests (inspiratory pressure and forced vital capacity [FVC]). These tests may be necessary as a reference to determine the optimal conditions for extubation as well as the need for postoperative mechanical ventilation[2,14].

The size of the tumor can produce complications in the airway or vascular obstruction during anesthetic induction. A review of the flow-volume curve can be indicated preoperatively. Maximal inspiratory and maximal expiratory capacity and the flow-volume curve can demonstrate the presence of a respiratory problem. The pre-operative management of these patients will be influenced by the surgical procedure and by the preference of the surgeon and anesthesia. Some of them are related to the dose of anticholinesterase in the morning of surgery to reduce the need for neuromuscular relaxants, while others continue with the treatment to avoid psychological stress of the patient and successive exacerbation of symptoms. If the patient is poorly controlled, pre-operative plasma administration may be of benefit for trans anesthetic control. The patient dependent on steroids will require perioperative coverage[2,15].

Patients undergoing major surgery must be admitted 48 h before the procedure. This allows the evaluation, monitoring of respiratory function, and the bar in addition to allowing the adjustment of anticholinesterase drugs and corticosteroids if indicated[1].

Effective respiratory physiotherapy and pulmonary health care are required due to an ineffective mechanism to expel secretions with cough, with application of humid gas that must be at 37°C in addition to performing maneuvers such as percussion, vibration, and postural drainage to remove bronchial secretions and achieve a better gas exchange from the hospital admission[1,16].

Regular aspiration serves not only to eliminate excess secretions from the oropharynx and trachea but also to stimulate cough, which is associated with a better independent prognosis of tidal volume or respiratory pattern[13,16].

Avoid atelectasis, because if they are extensive and do not respond to routine measures, therapeutic fibrobronchoscopy can be performed to promote the cleanliness of the respiratory tract[16].

The airway should be carefully evaluated, especially when MG is associated with a rheumatic disease due to the probable limitation of cervical extension and flexion. In addition, a large thymoma can cause distortion and compression of the trachea. To assess respiratory function, the most common form is FVC because it is reproducible and easy to carry out[1].

Pre-operative factors that mostly correlate with the need for prolonged mechanical ventilation after thymectomy include a FVC < 2.9 L, a history of chronic respiratory disease, myasthenia Grades III and IV, and a long history of disease (> 6 years). Care should also be taken during the pre-operative evaluation to exclude any associated autoimmune disease. Thyroid function tests are essential since approximately 15% of MG patients have some abnormality of this gland[1,17].

After the pre-operative evaluation, a complete explanation of the anesthetic procedure should be given to the patient, including the possibility of post-operative mechanical ventilation[1].

Many anesthesiologists avoid the use of sedatives in the pre-operative period, although they were shown to be safe to use[1].

Antimuscarinic agents such as glycopyrrolate are useful in reducing secretions before going to the operating room[1].

Corticosteroid therapy should be maintained and an additional dose of hydrocortisone administered on the day of surgery[1].

Balanced general anesthesia

The best time to perform elective surgery would be during a stable phase where the patient has used few drugs[4,18].

The type of anesthesia depends on the factors of admission, such as the severity of the disease and the type of surgery[1].

In case of opting for general anesthesia, a meticulous pre-operative assessment with adequate perioperative care will be required[1].

Drugs can be administered for sedation and anxiolysis, although it is recommended to do so until the patient enters the operating room and is monitored[4].

In the case of urgent intubation, it is recommended to follow the standard procedure for induction of rapid sequence (rocuronium 0.9-1.2 mg/kg if there are contradictions for succinylcholine)[4].

Routine monitoring of invasive blood pressure is recommended for anesthetic induction and maintenance[1,19].

Neuromuscular transmission must be permanently controlled throughout the procedure. The patient must be preoxygenated and induced with thiopental or propofol[1].

Several classes of depolarizing neuromuscular relaxants have been tried, to avoid the use of pre-operative pyridostigmine although studies such as that of Tripathi et al. demonstrated that patients who are discontinued with the administration of pyridostigmine on the day of surgery may develop respiratory distress requiring the administration of transoperative neostigmine[4].

Patients with MG have very few AChRs in good condition and therefore have an abnormal reaction to depolarizing neuromuscular blocking agents[4].

These responses are seen even in patients with purely ocular myasthenia. Due to the reduction in the functional number of postsynaptic AChR, there is often a relative resistance to the usual dose of succinylcholine. However, a Phase II block can later develop. When patients are treated with cholinesterase inhibitors, succinylcholine takes longer to inactivate with the risk of a very long neuromuscular block. Patients who do not receive cholinesterase inhibitors are relatively resistant to succinylcholine because normal nAChRs, to cause adequate depolarization, are lacking[4].

In contrast, patients with MG are extremely sensitive to nondepolarizing muscle blockers, although this sensitivity varies depending on the agent. Thus, only one-tenth of the dose of pancuronium may be necessary for relaxation, whereas in the case of atracurium, vecuronium or rocuronium, 30-40% of the normal dose may be required[1].

If the use of pyridostigmine is stopped, a smaller dose of the non-depolarizing neuromuscular relaxant will be used[20,21].

Because of the precaution in maintaining relaxation by non-depolarizing muscle relaxants, sugammadex was recently introduced as a binding agent designed to neutralize the effect of rocuronium steroid although it is also partially effective against vecuronium[12-33]. The effect basically produced by decreasing the number of free molecules of the relaxant after administration by binding the neuromuscular relaxant molecules. Therefore, it is possible to reverse a neuromuscular block 3 min after the administration of vecuronium or rocuronium and does not intervene with nAChR or anticholinesterase drugs[4,25,27,34].

The use of sugammadex in patients with MG has been described in three different publications in 2010. In these studies, a faster reversion was demonstrated without post-operative complications and with hospital discharge in a short period of time after surgery[22,24,33].

Most immunosuppressants do not have drug interactions with anesthetic drugs, excluding azathioprine, which prolongs the effects of succinylcholine and inhibits the efficacy of non-depolarizing agents[4,34].

Intravenous anesthetic agents versus inhaled anesthetics

In these patients, propofol has the theoretical advantage of a short duration of action without the presence of an effect on neuromuscular transmission. Opioid analgesics at therapeutic concentrations do not appear to depress neuromuscular transmission in the myasthenic muscle. However, central respiratory depression may be an opioid-related problem[4]. The introduction of short-acting opioids makes these drugs more feasible in these patients. Among them, remifentanil is an attractive drug due to its elimination and short half-life (9.5 min)[35]. The use of etomidate, ketamine, and thiopental has not produced incidents according to various reports[2,18].

We also compared the use of anestesia total intravenosa (total intravenous anesthesia) carried out with propofol and remifentanil versus general anesthesia balanced with desflurane and remifentanil for patients with MG. It was evidenced that in the group that received desflurane, there was a greater decrease in turn-over number (TOF) values compared to the group that received propofol[3].

Volatile anesthetics cause a reduction in neuromuscular transmission through different pathways; one of them is the inhibition of postsynaptic nAChR. Several studies have shown how the use of sevoflurane in these patients makes it possible to avoid neuromuscular relaxants during induction and intubation[1]. There have

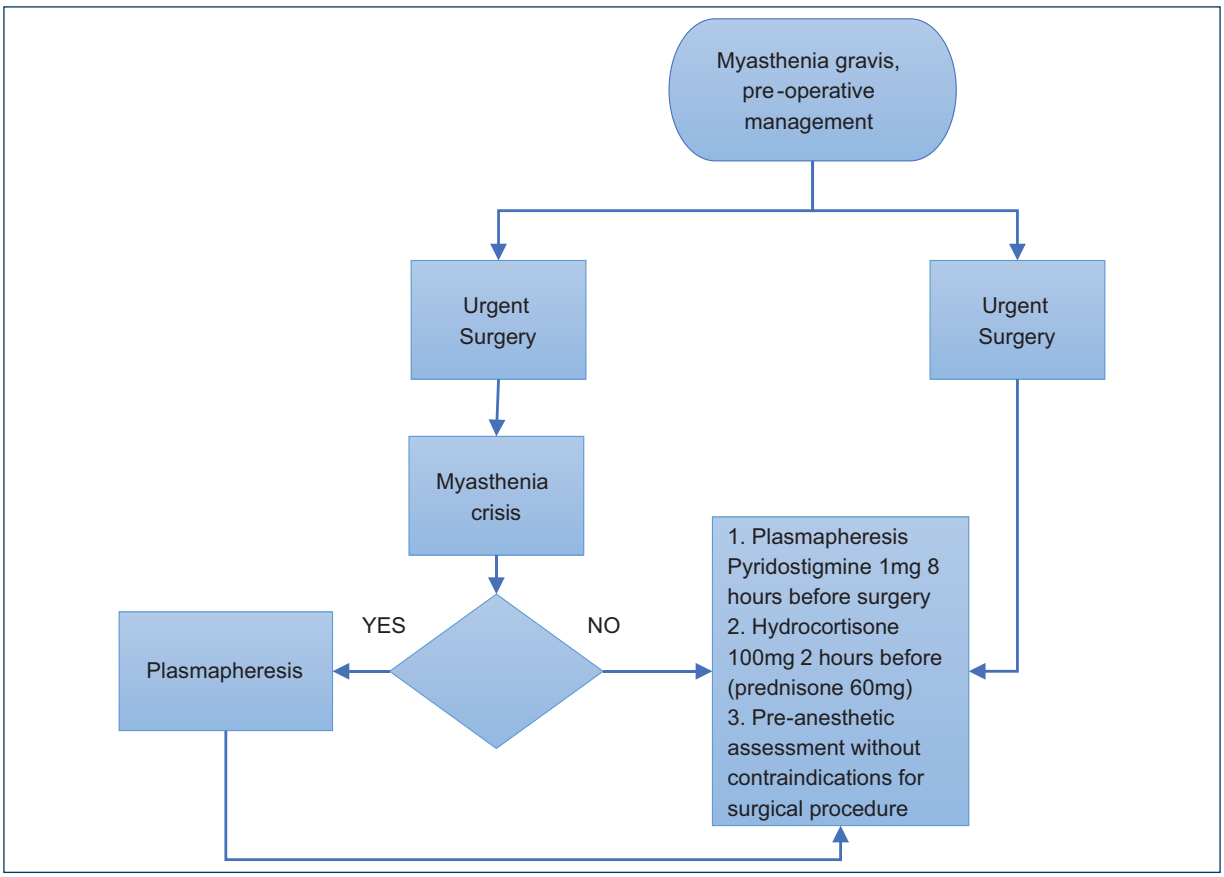

Figure 1. Pre-operative management.

even been reports of the decrease of TOF (train of four) during maintenance with sevoflurane increasing at the time of suspension[4,36,37].

Regional anesthesia

Patients treated with anticholinesterase drugs should be administered low doses of anesthetics during regional anesthesia[38].

Bupivacaine and ropivacaine are safe for thoracic surgery during and after it[39,40].

Many procedures that can be performed using peripheral nerve block are recommended for patients with MG[2]. The techniques of nerve blockade are safer and each time requires lower doses of local anesthetics[4].

Criteria for extubation

In patients with MG, it is crucial to verify that the patient has adequate spontaneous ventilation before extubation[4].

Different specific criteria have been proposed before the extubation of the myasthenic patient. Among them, an adequate level of consciousness, tidal volume of 5 ml/kg or more, spontaneous ventilation with PaCO2 of 50 mmHg (6.67 kPa) or less, PaO2 of 90 mmHg (12 kPa) or more, and respiratory rate of 30 breaths/min or less. Even so, the clinical evaluation of respiration with the criteria used routinely in all patients before extubation should be sufficient in myasthenic patients[41].

The most important thing is to ensure the absence of residual curarization before extubation, either using a TOF monitor in the unconscious patient or with a head elevation > 5 s in the conscious patient[41].

It is not routinely recommended to send patients to the intensive care unit (ICU) with mechanical ventilation to avoid increasing the risk of respiratory diseases[4].

Management of post-operative pain

The optimal management of pain is important because the stress caused by it can cause a myasthenic

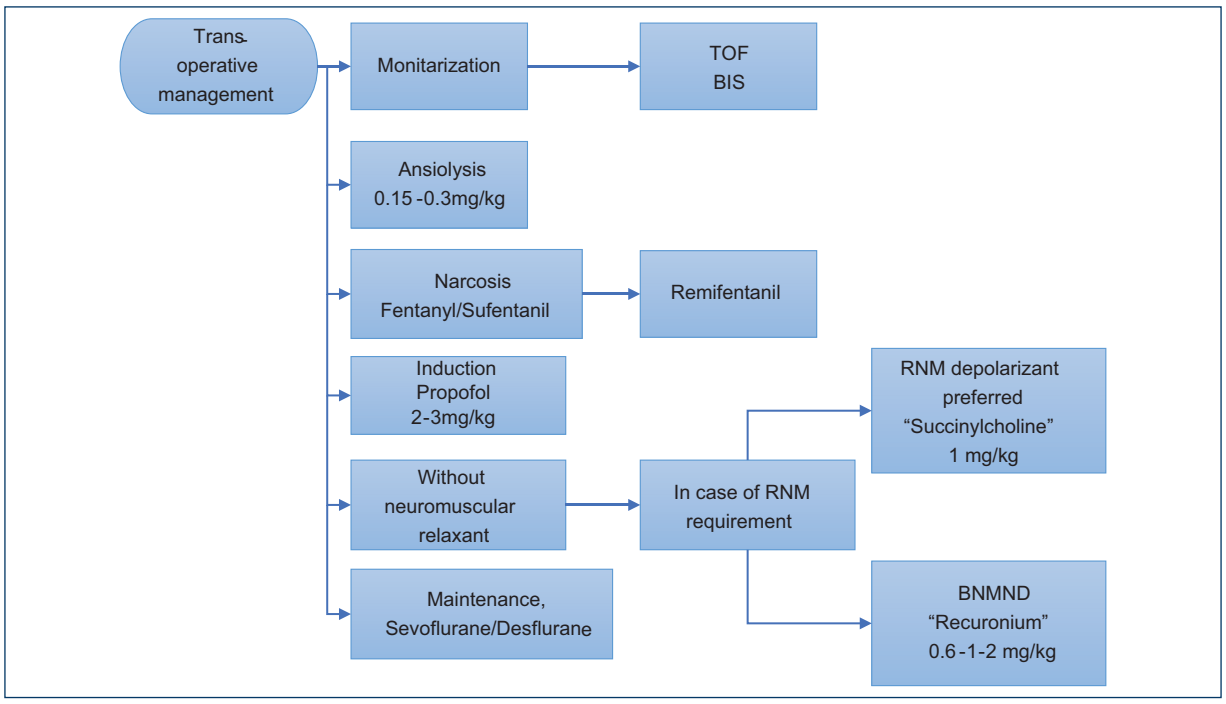

Figure 2. Transoperative management.

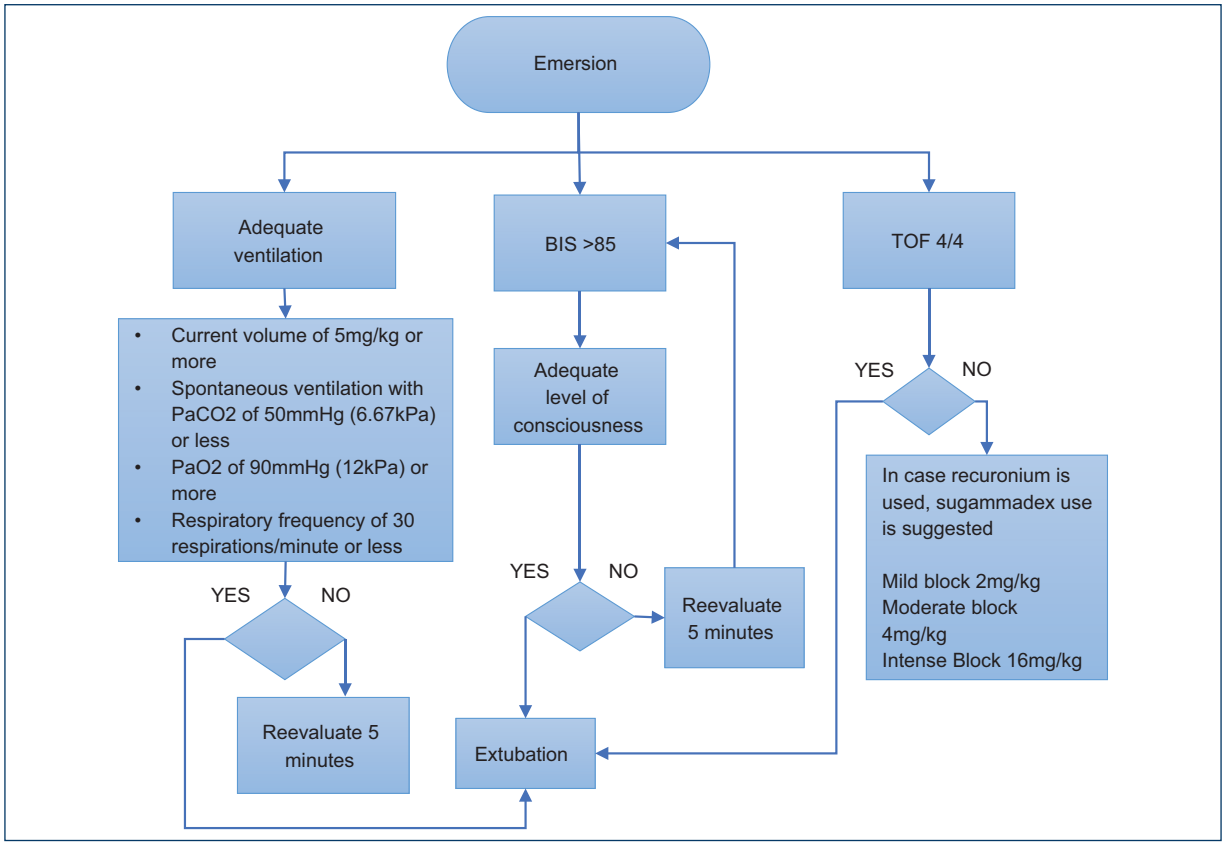

Figure 3. Criteria for extubation.

crisis leading to morbidity and mortality, and the probability of the patient's admission to the ICU. An appropriate method, whenever possible, is regional analgesia in the form of an epidural or peripheral block. In this way, the patient can avoid opiates and their harmful effects on ventilatory and gastrointestinal function.

Epidural anesthesia offers better control of post-operative pain with minimal or no opioid use and spontaneous ventilatory management by the patient, reducing the need for neuromuscular blockers during surgery[4].

The patient should resume the usual oral medication as soon as possible[4].

If intravenous/intramuscular opioids are necessary, small doses will be administered; preferably short-acting ones should be used until the pain relief is lasting[4].

Nonsteroidal anti-inflammatory drugs may be useful in the control of pain for patients with MG by reducing the need for opioids, although it can rarely eliminate it[4].

We designed three flow charts to perform more precise management in these patients, dividing it into pre-operative, transoperative management and criteria for extubation at the end of the surgery (Figs. 1-3).

Conclusions

In the management of patients with MG, the antecedents at admission are important. In case of emergency surgery with a patient in myasthenic or cholinergic crisis, pre-surgical plasmapheresis will avoid complications of extubation. Patients can receive anxiolysis and sedation while they are monitored and short-acting opioid-based analgesia is recommended. Muscle relaxants should be avoided, and whenever possible, early extubation is indicated.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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