Perioperative evaluation of myasthenia gravis

Ann. Ital. Chir., 2007; 78: 359-365

Alexander Cardone, Elisabetta Congedo, Paola Aceto, Rossella Sicuranza, Elisabetta Chinè, Francesca Caliandro, Germano De Cosmo

Istituto di Anestesiologia e Rianimazione Università Cattolica del Sacro Cuore, Roma

Perioperative evaluation of myasthenia gravis

Myasthenia gravis (MG) is the prototype of antibody mediated autoimmune disease and results from the production of autoantibodies against the acetylcholine receptor (AChR) of the neuromuscular synapse.
Adequate preoperative evaluation of the myasthenic patient must be carried out carefully. Age, sex, onset and duration of the disease as well as the presence of thymoma may determine the response to thymectomy. Specific attention should be paid to voluntary and respiratory muscle strength.
The preoperative preparation of MG patients is essential for the success of surgery. It depends on the severity of clinical status and changes if myasthenic patients receive anticholinesterase therapy. Myasthenic patients may have little respiratory reserve, and hence depressant drugs for preoperative premedication should be used with caution and avoided in patients with bulbar symptoms.
The anaesthetic management of myasthenic patient must be individualized in according to the severity of the disease and the type of surgery required. The use of regional or local anaesthesia seems warranted whenever possible.
General anaesthesia can be performed safely when patient is optimally prepared and neuromuscular transmission is adequately monitored during and after surgery.
Adequate postoperative pain control, pulmonary toilet, and avoidance of drugs that interfere with neuromuscular transmission will facilitate tracheal extubation.
Myasthenia gravis is a disease with many implications for the safe administration of anaesthesia. The potential for respiratory compromise in these patients requires the anaesthesiologist to be familiar with the underlying disease state, as well as the interaction of anaesthetic and non-anaesthetic drugs with MG.

KEY WORDS: Myasthenia gravis, Neuromuscular blocking drugs, Preoperative anaesthesic evolution.

Introduction

An optimal perioperative management of patients with Myasthenia Gravis (MG) requiring thymectomy needs careful preparation and evaluation.
This evaluation includes investigation of concomitant cardiac and pulmonary autoimmune disease and optimization of clinic management of MG.
Specific attention should be applied for intraoperative monitoring, use of muscle relaxants and other drugs used during general anesthesia and also for premedication.
It is essential, during postoperative period, to achieve a good control of pain and ventilatory function must be monitored carefully after surgery. Many clinicians prefer to avoid the use of anticholinesterase. A correct management increases the possibility of successful and improves clinical outcome.

For correspondence: Alexander Cardone, MD, Catholic University of Sacred Heart, Institute of Reanimation and Anaesthesiology, Policlinic "A. Gemelli", Largo A. Gemelli 8, 00168 Rome, Italy.

Myasthenia Gravis

MG is the prototype of antibody mediated autoimmune disease. It may be associated with other disorders of autoimmune origin such as thyroid hypofunction, rheumatoid arthritis, and systemic lupus erythematosus [1]. Myasthenia gravis results from the production of autoantibodies against the acetylcholine receptor (AChR) of the neuromuscular synapse [2-4]. However, it is not yet known what triggers the autoimmune response or what permits it to be sustained. An immunoregulatory defect has been postulated and there is evidence of genetic predisposition [5,6]. Using the most sensitive assays, AChR antibodies are detected in the 85-90% of myasthenic patients [4]. The majority of AChR antibodies belongs to the IgG

class. Antibody-negative patients are those with mild or localized myasthenia, and may represent merely one end of the spectrum of myasthenia gravis [3]. The available evidence suggests both that individual myasthenic patients have heterogenous populations of AChR antibodies, and that there is only limited sharing of idiotypes among patients [3]. Most of the antibodies bind to the main immunogenic region of the alpha subunit of the endplate receptors [5]. Thus, MG is largely a postjunctional disorder characterized by functional reduction of AChR.

The thymus and its cellular products, the T cells, are involved in many aspects of autoimmune diseases. It could represent an unique site of autosensitization against AChR antigenic determinants and myoid cells bearing AChR are present in the normal thymus [7]. In myasthenia gravis one may assume that T cells become sensitized against the myoid AChR when they are present in the thymus at a critical stage of maturation [8]. The immunoregulatory T cells play a key role in the pathogenesis of MG. The macrophage-associated AChR interacts with ACh-R helper T cells, which proliferate and produce factors that promote anti-AChR antibody production by B cells. According to the network theory, anti-idiotypic antibodies can initiate or modify the immune response. Anti-idiotypes antibodies against AChR have been reported in MG [3]. However, their role in the initiation and perpetuation of MG remains to be confirmed.

Several arguments suggest the existence of a close relationship between MG and thymus function [9]. The disease is frequently associated with morphological abnormalities of the thymus gland (hyperplasia or thymoma), and thymectomy has been reported to improve the symptoms of the disease. Fifteen to twenty percent of patients with MG have thymomas. Thymomas are more likely to occur in patients older than thirty years of age, whereas thymic hyperplasia frequently happens in younger patients [9]. MG is frequently a cause of cronic and severe disability and in the past was characterized by an high mortality. The improvement of treatment and critical care ave changed long-term prognosis and nowadays expectation of life is approximately normal.

Anaesthetic management

The anaesthetic management of myasthenic patient must be individualized in according to the severity of the disease and the type of surgery required. The use of regional or local anaesthesia seems warranted whenever possible. Whenever local or regional anaesthesia is used, the dose of the local anaesthetic may be reduced in patients to decrease the possible effects of anaesthetics on neuromuscular transmission [1].

This may be particularly important when ester local anaesthetics are administered to patients receiving anticholinesterase therapy. General anaesthesia can be performed safely when patient is optimally prepared and neuromuscular transmission is adequately monitored during and after surgery [10-12].

Preoperative evaluation

Adequate preoperative evaluation of the myasthenic patient must be carried out carefully. Age, sex, onset and duration of the disease as well as the presence of thymoma may determine the response to thymectomy[1]. Preoperative evaluation of the myasthenic patient includes review of the severity of patient's disease and the treatment regimen. Specific attention should be paid to voluntary and respiratory muscle strength. The patient's ability to protect and maintain a patent airway postoperatively may be compromised if any bulbar involvement exists preoperatively. The ability to cough and clear secretions may be compromised as well. Preoperative evaluation includes analysis of concomitant affections and complications of underlying myopathy (through thorax radiography, pulmonary function tests quantifying respiratory muscle strength and arterial blood gas analysis). Cardiac evaluation by ECG, echocardiogram and, if necessary, Holter and cardiac scintigraphy are required.

Preoperative evaluation should include pulmonary function studies. Preoperative respiratory function tests must be performed because chronic respiratory disease and a preoperative vital capacity <2.9 L are two of the predictive criteria for postoperative respiratory support [1]. In addition to vital capacity (VC), maximum expiratory force (MEF) should be measured, both before and after cholinergic inhibition, if the patient is receiving such medication and can tolerate its withdrawal for 6-8 hours (1.5 to 2 mg neostigmine intramuscularly for adults in association with 0.4 mg atropine). The dual before and after measurements give an indication of the deficits that may be masked by the cholinergic inhibitors and thus confirm the need for preoperative therapy [13]. The MEF measurement is as easy to perform as the VC, is an excellent measure of cough effectiveness (an important determination), and is much more sensitive and reliable than the CV in the evaluation of myasthenic patients, both preoperatively and in the early postoperative period. An MEF of less than 40 to 50 cm H_2O indicates a potential for postoperative respiratory complications and respiratory failure [14,15].

Myasthenia gravis may be classified on the basis of skeletal muscles involved and severity of the symptoms. The various stages of disease have been classified by Ossermann and Genkins resulting the following four types. Type I is limited to involvement of the extraocular muscles. Type IIA is a slowly progressive and mild form of skeletal muscle weakness which spares respiratory muscles. Type IIB is a more severe and rapidly pro-

gressive form of skeletal muscle weakness. Type III is characterized by an acute onset and rapid deterioration that is associated with an high mortality. Type IV is a severe form resulting from progression of Type I and II [1].

Preoperative preparation

The preoperative preparation of MG patients is essential for the success of surgery. It depends on the severity of clinical status and changes if myasthenic patients receive anticholinesterase therapy. Depending on the strength of MG stage, anticholinesterase therapy may be suspended or reduced till four days before surgery. In patients with I or II stage of MG can be possible a complete interruption of treatment. The other stages will be individually evaluated. Actually the treatment for stage II of MG is plasmapheresis or intravenous immunoglobulin. Other forms of targeted therapy should be considered as they become available. Immunosuppression is also used although its role is less well-defined [16-18].
Anticholinesterase inhibition alone should not be used in the preoperative preparation of patients with even mild respiratory or oropharyngeal weakness, as these agents only temporarily (hours) mask the weakness of MG. Thus, treated patients can be expected to have a high rate of postoperative respiratory complications.
Also, anticholinesterases can inhibit plasma cholinesterase activity with a subsequent decrease in the metabolism of ester local anaesthetics [1].
It is controversial whether anticholinesterase therapy should be maintained or discontinued before and after surgery.
Corticosteroid medications are maintained to be tapered and discontinued postoperatively.

Premedication

Myasthenic patients may have little respiratory reserve, and hence depressant drugs for preoperative premedication should be used with caution and avoided in patients with bulbar symptoms. Usually, myasthenic patients can be premedicated with atropine (0.6 mg *i.m.*) and only diazepam (5 mg *p.o.*) can be used for sedation. It is controversial whether anticholinesterase therapy should be maintained or discontinued before and after surgery [40]. Anticholinesterases potentiate vagal responses and hence adequate atropinization must be ensured. It is advisable to inform patients that postoperative tracheal intubation and respiratory support might be required.

Introperative management

Monitoring

Intraoperative monitoring includes electrocardiogram, arterial blood pressure monitoring, pulse oximetry, end-tidal CO_2 ($EtCO_2$) and expiratory gas analysis. Neuromuscular transmission must be carefully monitored during surgery by periphered nerve stimulation to titrate the necessary dose of muscle relaxants, and to ensure complete reversal of neuromuscular block at the end of surgery [29,30,34,35]. Neuromuscular transmission can be monitored with a TOF-Guard device. Monitoring should be continued postoperatively for early detection of neuromuscular dysfunction.

Anaesthetic management

The anaesthetic management of the myasthenic patient must be individualized to the severity of the disease and the type of surgery. The use of regional or local anaesthesia seems warranted whenever possible [1]. Whenever local or regional anaesthesia is used, the dose of the local anaesthetic may be reduced in patients to decrease the possible effects of anaesthetics on neuromuscular transmission.
General anaesthesia can be performed safely when patient has been optimally prepared and neuromuscular transmission is adequately monitored during and after surgery [1]. The safe use of general anaesthesia requires attention for monitoring the patient and understanding the variable responses that he may have to many drugs. EMG and mechanomyograph are the preferred methods for monitoring neuromuscular transmission. They record control values to compare these with those elicited throughout surgery and postoperatively. Several general anaesthetic techniques have been proposed, although none has been proven to be superior to the others [20]. Some prefers to avoid muscle relaxants altogether and to use potent inhaled agents both to facilitate tracheal intubation and provide muscle relaxation for surgery. These agents allow neuromuscular transmission to recover and are characterized by a rapid elimination at the end of surgery. By theory, desflurane and sevoflurane may offer some advantages, due to their low blood solubility. Sevoflurane is probably superior to desflurane, due to its lower incidence of excitatory airway reflexes during inhalational induction. Others titrate small doses (10-25% of the ED95) of intermediate-acting relaxants for both intubation and surgical relaxation, if required [20]. The decision whether to reverse residual neuromuscular blockade at the end of surgery is controversial. Some argue that the presence of anticholinesterases and antimuscarinics will confuse efforts to differentiate weakness due to inadequate neuromuscular transmission from cholinergic crisis in the recovery room. They prefer spontaneous recovery and extubation when the patient has demonstrated adequate parameters for it (i.e., head-lift, tongue protrusion) [20].

Intravenous Anesthetic Agents

Anesthetic management using barbiturates and propofol for myasthenic patients without untoward effects have

been described [21,22]. Propofol has the theoretic advantages of short duration of action without effect on neuromuscular transmission. Opioid analgesics in therapeutic concentrations do not appear to depress neuromuscular transmission in myasthenic muscle [23,24]. However, central respiratory depression may be a problem with opioids. The introduction of short-acting opioids makes these drugs more titratable in myasthenic patient.

Neuromuscular blocking drugs

Neuromuscular blocking drugs act by interrupting neuromuscular transmission at the level of the nicotinic acetylcholine receptors in the motor end plate. Their action way can be classified as antagonist (nondepolarizing) or agonist (depolarizing), both producing blockade [36].

Because of the decreased number of AChR and/or their functional blockade by AChR antibodies, succinylcholine may not effectively depolarize the endplate resulting in "resistance". The ED50 and ED95 in myasthenic patients is 2.0 and 2.6 times normal, respectively [11]. Thus, high doses of succinylcholine may be required for rapid sequence tracheal intubation in a patient with MG. The endplate potential may not reach the threshold required for inducing depolarizing "phase I" block, and hence succinylcholine may readily induce phase II block [37]. Also, it is possible that the phase II block seen in some cases is due to the decreased plasma cholinesterase activity induced by the preoperative anticholinesterase administration. Anticholinesterase can decrease the plasma cholinesterase activity [48], with a subsequent delayed hydrolysis of succinylcholine and potentiation of neuromuscular block [1]. The reduction of the number of ACh receptors at the neuromuscular junction, and the consequent reduction of the "safety margin" [38] makes myasthenic patients extremely sensitive to nondepolarizing muscle relaxants. There is a large spectrum in the severity of the disease in patients with myasthenia gravis, and thus muscle relaxant requirements are also extremely variable. One tenth of the normal paralysing dose may be sufficient to paralyse a patient with MG which is why many anaesthetists avoid the administration of nondepolarizing relaxants. However, this policy may not be applied to intermediate-acting relaxants such as atracurium and vecuronium. Both atracurium [29,30] and vecuronium [28,34,35,39] are rapidly eliminated, and their dose can be titrated to achieve the required neuromuscular blockade that can be completely reversed at the termination of the surgical procedure.

Nondepolarizing agents can be used with careful monitoring of neuromuscular transmission, preferably with electromyogram (EMG) or mechanomyogram (MMG), which measure the evoked electrical or mechanical responses following electrical stimulation of a peripheral motor nerve. Stimuli can be delivered in trains-of four (TOF) stimuli (2 Hz) at 10-second intervals. In the absence of a neuromuscular block, a control response is obtained. This control "twitch" is designated Tc [20]. In the absence of a neuromuscular block, all responses should be of equal magnitude. Thus, with TOF stimulation, the control, first, second, third and fourth responses are equal (Tc=T1=T2=T3=T4). In the presence of a nondepolarizing block, Tc > T 1 and T4<T3<T2<T1 [20]. The ratio of T4 /T1 is called the fade ratio and is used to assess the extent of a nondepolarizing block. In the presence of a depolarizing or phase I block (due to succinylcholine) Tc>T1 but T1=T4, i.e., there is no fade with this type of block. Sometimes a phase I block changes in nature and takes on the characteristics of a nondepolarizing block (i.e., fade develops) [20].

The latter block is called a phase II block. In myasthenic patients, the ED95 for vecuronium ranges from 40% (17 mcg/kg vs. 24 mcg/kg) [27] to 55% (20 mcg/kg vs. 36 mcg/kg) [28] of that in normal controls. There are wide variations in responses among myasthenics. Elimination of vecuronium is not altered. Wide variability in requirements was also noted for atracurium [29]. The ED95 was 58% (0.14 mg/kg vs. 0.24 mg/kg) of the value for normal patients [30]. Myasthenic patients are similarly sensitive to cisatracurium, as evidenced by a more rapid onset and more marked neuromuscular block compared with control patients [31]. Increased sensitivity to mivacurium has also been reported [32]. Recovery was prolonged (recovery index 25-75% for T1 of 20.5 minutes vs 11.9 minutes) in a patient receiving pyridostigmine [33].

Pyridostigmine inhibits the metabolism of mivacurium and therefore increases recovery times when mivacurium is administered. Therefore, it should be used with caution in patients receiving pyridostigmine on the morning of surgery.

Total intravenous anesthesia (TIVA)

Total intravenous anesthesia (TIVA) for the management of myasthenics has been reported [21]. In the authors experience, hemodynamic instability in older patients makes this approach difficult, whereas younger patients usually tolerate it without difficulty. The use of remifentanil as part of TIVA may alleviate some of the hemodynamic instability.

Regional or local anesthetic

When possible, many clinicians prefer to utilize regional or local anesthetic techniques. Epidural techniques offer the advantage of postoperative pain control with minimal or not opioid use. The safe and successful use of thoracic epidural blockade with bupivacaine for intraoperative anesthesia and postoperative analgesia for transsternal thymectomy has been reported [25,26]. Spinal anesthesia has the advantage of reduced drug dosage, whereas epidural techniques facilitate easier control of blockade level and may obviate the need for opioids in postoperative pain management. However, potentiation of neuromuscular blocking drugs by local anesthetics has been reported.

Postoperative management

Postoperative ventilation

Ventilatory function must be monitored carefully after surgery. Despite the enormous number of studies in the literature, few of these correlate tests of neuromuscular function with adequate ventilation. It has been shown recently in normal patients that many of the recommended tests such as maintained response to tetanic stimulation of a peripheral nerve can return to normal, while the pharyngeal and neck muscles necessary to protect the airway can still be partially paralysed [40]. The different response of peripheral versus bulbar muscles may be more evident in myasthenic patients, particularly those suffering from bulbar and/or respiratory muscle weakness. Sustained respiratory muscle strength should be confirmed before extubation of the trachea and resumption of spontaneous ventilation [1]. Patients should be considered partially paralysed until they wake up and can lift their head for five seconds. An inspiratory force exceeding - 25 cm H_2O may be used as a criterion of adequate respiratory function. Myasthenic patients may be at increased risk of developing postoperative respiratory failure. Several authors have proposed criteria for predicting which patients will require prolonged postoperative mechanical ventilation [1].

To predict the need for postoperative ventilation, Leventhal et al proposed a scoring system which takes into account duration of myasthenia gravis for longer than six years (12 points). Duration of MG proved to have the greatest value in predicting the need for ventilatory support as an history of chronic respiratory disease other than respiratory dysfunction directly due to MG (10 points) a dose of pyridostigmine greater than 750 mg per day, 48 hr before operation (8 points) and a preoperative vital capacity < 2.9 L (4 points) [41].

These risk factors were weighted according to their significance as predictors; a total score of ten points identified those patients likely to need postoperative pulmonary ventilation for more than three hours. The Leventhal scoring system had a sensitivity of 22.2%, a specificity of 77.8%, a positive predictive value of 25% and a negative predictive value of 75% for assessing the need of postoperative ventilatory support [42].

Adequate postoperative pain control, pulmonary toilet, and avoidance of drugs that interfere with neuromuscular transmission will facilitate tracheal extubation. All patients with MG should be closely monitored postoperatively in the postanesthesia care unit or the surgical intensive care unit, where respiratory support can be immediately reinstituted. Weakness after surgery presents a special problem in MG patients. The differential diagnosis includes myasthenic crisis, residual effects of anaesthetic drugs, non-anaesthetic drugs interfering with neuromuscular transmission and cholinergic crisis.

Cholinergic Crisis

Cholinergic crisis results from an excess of acetylcholine at the nicotinic and muscarinic receptors. It usually results from administration of excessive anticholinesterase drugs doses. Nicotinic over-stimulation results in involuntary twitching, fasciculations, and weakness (sometimes leading to respiratory arrest) [20]. The weakness results from an inability to coordinate muscle contraction and relaxation. When the muscarinic effects are obvious, the diagnosis is easily made [20]. Antimuscarinics and respiratory support are indicated. When acetylcholinesterase inhibition in conjunction with antimuscarinics has been used to reverse residual neuromuscular blockade, weakness and fasciculations may predominate in the absence of muscarinic symptoms. To differentiate this from myasthenic crisis, an edrophonium test may be administered. Also, in a myasthenic crisis, the pupils will be dilated. In the absence of muscarinic symptoms, simply allowing the patient to recover clinically, without elaborate testing, while maintaining mechanical respiratory support, constitutes a safe and practical approach [20]. For these reasons, many clinicians prefer to avoid the use of muscle relaxants, or if they do so, to allow the neuromuscular block to recover spontaneously, avoiding the use of anticholinesterase in the immediate postoperative period.

Conclusions

Myasthenia gravis is a disease with many implications for the safe administration of anaesthesia. The potential for respiratory compromise in these patients requires the anaesthesiologist to be familiar with the underlying disease state, as well as the interaction of anaesthetic and non-anaesthetic drugs with MG [20]. A standardized combined anaesthetic technique (without muscle relaxants) provided optimal operating conditions, improved patient comfort following trans-sternal and thoracic incision, avoided the need for postoperative ventilatory support and resulted in fewer admissions in ICU and shorter duration of hospital stay.

Riassunto

La Miastenia Gravis (MG) è il prototipo delle malattie autoimmuni anticorpo-mediate. È caratterizzata da debolezza della muscolatura scheletrica e da un andamento fluttuante, con l'alternarsi di fasi di remissione e di esacerbazione della sintomatologia e può essere associata ad altre patologie a genesi autoimmune.

Essa consegue alla produzione di anticorpi rivolti contro il recettore per l'acetilcolina, situato nel sito post-sinaptico della giunzione neuromuscolare, causando un fallimento della trasmissione e determinando un'interruzione del potenziale d'azione.

Un'ottimale gestione perioperatoria dei pazienti con MG, sottoposti a timectomia, richiede un'attenta preparazione e valutazione.
Quest'ultima include la valutazione per eventuali malattie autoimmuni concomitanti, sia cardiache che polmonari e l'ottimizzazione della gestione clinica della miastenia.
Il piano anestesiologico del paziente miastenico deve essere costituito sulla base della severità della malattia e del tipo di chirurgia. L'anestesia regionale o locale sembra offrire buone garanzie quando la sua attuazione è possibile. L'anestesia generale può essere eseguita con sicurezza a condizione che la preparazione del paziente sia ottimale e la trasmissione neuromuscolare sia adeguatamente monitorizzata durante e dopo la chirurgia.
Particolare attenzione va posta nel monitoraggio intraoperatorio e nell'uso dei miorilassanti e degli altri farmaci che vengono impiegati durante l'anestesia generale e nella premedicazione.
Nel postoperatorio è essenziale ottenere un buon controllo del dolore, ottimizzare la gestione della ventilazione e utilizzare attentamente gli agenti anticolinesterasici. L'ottimizzazione di queste procedure aumenta le possibilità di successo e consente di ottenere un'ospedalizzazione scevra da complicanze.

References

1) Baraka A: *Anesthesia and myasthenia gravis.* Middle East J Anesthesiol, 1993; 12(1):9-35.

2) Drachman DB: *Myasthenia gravis.* N Engl J Med, 1978; 298:136-42.

3) Drachman DB, De Silva S, Ramsay D, Pestronk A: *Humoral pathogenesis of myasthenia gravis.* Ann N Y Acad Sci, 1987; 505:90-105.

4) Lindstrom JM, Seybold ME, Lenon VA, et al: *Antibody to acetylcholine receptor in myasthenia gravis. Prevalence, clinical correlates, and diagnostic value.* Neurology, 1976; 26:1054-59.

5) Shinomiya N, Segawa M, Yata L: *In vitro study of T-cells regulating anti-acetylcholine receptor antibody formation in myasthenia gravis.* Ann N Y Acad Sci, 1981; 377:882-83.

6) Behan PO, Shields J; *Genetics.* In: Lisak R, Barchi R (Eds.): *Myasthenia Gravis.* Philadelphia:W. B. Saunders, 1982; 37-50.

7) Raimond F, Morel E, Bach JF*: Evidence for the presence of immunoreactive acetylcholine receptors on human thymus cells.* J Neuroimmunol, 1984; 6: 31-40..

8) Muller-Hermclink HK, Kirchner T, Hoppe F, Demel S: *Thymic myoid cells-stimulants and/or targets of autoimmune myasthenia gravis. In:* De Baets MH, Dosterhufs HJGH, Toyka KV.:Monographs in Allergy, *Myasthenia Gravis*, New York: Karger, 1988; 25:68-74.

9) Berrih-Aknin S, Morel E, Raimond F, et al*: The role of the thymus in myasthenia gravis: immunohistological and immunological studies in 115 cases.* Ann N Y Acad Sci ,1987; 505:50-70.

10) Stoelting RK, Dierdorf SF, McCommon RL: *Myasthenia Gravis.* In*: Anesthesia and Co-Existing Disease*, 2nd ed, New York: Churchill Livingstone, 1988; 626-30.

11) Miller J, Lee C: *Muscle diseases.* In: Katz J, Benumof J, Kadis LB (Eds.): *Anesthesia and Uncommon Diseases.* Philadelphia: W.B. Saunders Company, 1981; 530-61.

12) Dierdorf SF*: Rare co-existing diseases.* In: Barash PG, Cullen BF, Stoelting RK (Eds.). *Clinical Anesthesia*, Philadelphia: J.B. Lipincott Company, 1989; 441-42.

13) Jaretzki A, III: *Thymectomy for myasthenia gravis: Analysis of controversies-patient management.* Neurologist, 2003; 9(2):77-92.

14) Krucylak PE, Naunheim KS*: Preoperative preparation and anesthetic management of patients with myasthenia gravis.* Semin Thorac Cardiovasc Surg. 1999; 11(1):47-53 (Review).

15) Younger DS, Braun NMT, Jaretzki A, III, et al: *Myasthenia gravis: Determination for independent ventilation after transsternal thymectomy*. Neurology. 1984; 34:336-40.

16) Mulder DM: *Extended transsternal thymectomy.* Chest Surg Clin N Am, 1996; 6:95-105.

17) D'Empaire G, Hoaglin DC, Perlo VP, et al: *Effect of prethymectomy plasma exchange on postoperative respiratory function in myasthenia gravis.* J Thorac Cardiovasc Surg. 1985; 89:592-96.

18) Gotti P, Spinelli A, Marconi G, et al: *Comparative effects of plasma exchange and pyridostigmine on expiratory muscle strength and breathing pattern in patients with myasthenia gravis.* Thorax, 1995; 50:1080-86.

19) Miller J, Lee C: *Muscle diseases.* In: Katz J, Benumof J, Kadis LB (Eds.): *Anesthesia and Uncommon Diseases.* Philadelphia: W.B. Saunders Co, 1981;530-61.

20) Abel M, Eisenkraft JB: *Anesthetic implications of myasthenia gravis.* Mt Sinai J Med, 2002; 69(1-2):31-37.

21) O'Flaherty D, Pennant JH, Rao K, et al: *Total intravenous anesthesia with propofol for transsternal thymectomy in myasthenia gravis.* J Clin Anesth, 1992; 4:241.

22) Lin CC, Chen MF, Chen HM, et al. : *Propofol anesthesia in a patient with myasthenia gravis: A case report.* Acta Anaesthesiol Sin, 1996; 34:89-92.

23) Kin YI, Howard JF, Sanders DB: *Depressant effects of morphine and meperidine on neuromuscular transmission in rat and human myasthenic muscles.* Soc Neurosci Abstr, 1979; 5:482-502.

24) Sanders DB, Kim YI, Howard JF, et al.: *Intercostal muscle biopsy studies in myasthenia gravis: Clinical correlations and the direct effects of drugs and myasthenic serum.* Ann N Y Acad Sci, 1981; 377:544-66.

25) Akpolat N, Tilgen H, Gursoy F, et al.: *Thoracic epidural anaesthesia and analgesia with bupivacaine for transsternal thymectomy for myasthenia gravis.* Eur J Anaesthesiol, 1997; 14:220:23.

26) Kawamata M, Miyabe M, Nakae Y, et al: *Continuous thoracic epidural blockade in combination with general anesthesia with nitrous oxide, oxygen, and sevoflurane in two patients with myasthenia gravis.* Masui, 1993; 42:898-901.

27) Nilsson E, Meretoja OA: *Vecuronium dose-response and maintenance requirements in patients with myasthenia gravis.* Anesthesiology, 1990; 73:28-32.

28) Eisenkraft JB, Book WJ, Papatestas AE, et al:. *Sensitivity to vecuronium in myasthenia gravis: A dose response study.* Can J Anaesth. 1990; 37:301-6.

29) Baraka A, Dajani A: *Atracurium in myasthenics undergoing thymectomy*. Anesth Analg , 1984; 63:1127-130.

30) Smith CE, Donati, F, Bevin DR: *Cumulative dose-response curves for atracurium in patients with myasthenia gravis*. Can J Anaesth, 1989; 36:402-6.

31) Baraka A, Siddik S, Kawkabani N: *Cisatracurium in a myasthenic patient undergoing thymectomy*. Can J Anaesth, 1999; 46:779-82.

32) Seigne RD, Scott RP: *Mivacurium chloride and myasthenia gravis*. Br J Anaesth, 1994; 72:468-69.

33) Paterson IG, Hood JR, Russel SH, et al.: *Mivacurium in the myasthenic patient*. Br J Anaesth, 1994; 73:494-98.

34) Hunter JM, Bell CF, Florence AM, Jones RS, Utting JE: *Vecuronium in the myasthenic patient*. Anaesthesia, 1985; 40:848-53.

35) Buzello W, Noeldge G, Krieg N, Brobmann GF: *Vecuronium for muscle relaxation in patients with myasthenia gravis*. Anesthesiology, 1986; 64:507-9.

36) Book WJ, Abel M, Eisenkraft JB: *Adverse effects of depolarizing neuromuscular blocking agents. Incidence, prevention and management*. Drug Safety, 1994; 10:331-49.

37) Eisenkraft JB, Book J, Mann SM, Papatestas AE. Hubbard M: *Resistance to succinylcholine in myasthenia gravis: A dose-response study*. Anesthesiology, 1988; 69:760-63.

38) Waud BE, Waud D: *The relation between tetanic fade and receptor occlusion in the presence of competitive neuromuscular block*. Anesthesiology, 1971; 35:456-64.

39) Baraka A, Tabboush: *Neuromuscular response to succinylcholine-vecuronium sequence in three myasthenic patients undergoing thymectomy*. Anesth Analg, 1991; 72:827-30.

40) Pavlin EG, Holle RH, Schoene RB: *Recovery of airway protection compared with ventilation in humans after paralysis with curare*. Anesthesiology, 1989; 70:381-85.

41) Leventhal SR, Orkin FK, Hirsh RA: *Prediction of the need for postoperative mechanical ventilation in myasthenia gravis*. Anesthesiology, 1980; 53:26-30.

42) Chevaqlley C, Spiliopoulos A, de Perrot M, Tschopp JM, Licker M: *Perioperative medical management and outcome following thymectomy for myasthenia gravis*, Can J Anest, 2001; 48(5):446-51.

43) Eisenkraft JB, Papatestas AE, Pozner JN, Fagerstrom R, Genkins G: *Predictors of respiratory failure following transcervical thymectomy*. Ann N Y Acad Sci, 1987; 505:888-90.