Perioperative medical management and outcome following thymectomy for myasthenia gravis

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Purpose: To describe the evolution of the perioperative management of myasthenia gravis (MG) patients undergoing thymectomy and to question the need for systematic postoperative ventilation.

Clinical features: We collected data retrospectively from 36 consecutive MG patients who underwent thymectomy over a 21-yr period, via transthoracic, -cervical or -sternal incisions ($n=5$, $n=7$, $n=24$, respectively). From 1980 to 1993, a balanced anesthetic technique ($n=24$) included various inhalational agents with opiates and myorelaxants (in eight cases); 22 patients were admitted to the intensive care unit (ICU). Since 1994, *iv* propofol was combined with epidural bupivacaine and sufentanil ($n=12$); all patients were admitted to the postanesthesia care unit.

Short-term postoperative ventilation (median time four hours, range from three to 48 hr) was required in eight patients who had longer hospital stay (median stay=12 days, range (8–28) *vs* five days (4–15) for patients with early extubation, $P<0.05$) but similar clinical improvement six months after thymectomy.

Postoperative ventilatory support was required more frequently when a balanced anesthetic technique was used (odds ratio=4.2 (1.1–9.7), $P=0.03$) and particularly when myorelaxants were given (odds ratio=13.9 (2.1–89.8), $P=0.009$). Leventhal's scoring system had low sensitivity (22.2%) and positive predictive values (25%).

Conclusions: Our data show that the severity of MG failed to predict the need for postoperative ventilation. A combined anesthetic technique was a safe and cost-effective alternative to balanced anesthesia as it provided optimal operating conditions and resulted in fewer admissions in ICU and shorter hospital stays.

Objectif : *Décrire l'évolution du traitement périopératoire de patients atteints de myasthénie grave (MG) subissant une thymectomie et discuter de la nécessité de la ventilation postopératoire systématique.*

Éléments cliniques : *Nous avons recueilli rétrospectivement des données concernant 36 patients successifs atteints de MG qui ont, sur une période de 21 ans, subi une thymectomie selon différentes techniques : transthoracique, cervicale ou sternale ($n=5$, $n=7$, $n=24$, respectivement). De 1980 à 1993, on note qu'une technique anesthésique balancée ($n=24$) comprenait différents anesthésiques par inhalation, des opiacés et des myorelaxants (chez huit cas) et que 22 patients ont été admis à l'unité des soins intensifs (USI). À partir de 1994, le propofol iv a été combiné à la bupivacaïne et au sufentanil péridiuraux ($n=12$) et tous les patients ont été admis en salle de réveil.*

La ventilation postopératoire de courte durée (temps médian de quatre heures, variant de trois à 48 h) a été nécessaire chez huit patients qui sont restés plus longtemps à l'hôpital (séjour médian de 12 jrs, variant de 8 à 28 jrs vs cinq jours (4–15) pour les patients qui ont connu une extubation précoce, $P<0,05$) mais l'évolution clinique était similaire six mois après la thymectomie.

L'assistance ventilatoire postopératoire a été plus souvent nécessaire avec l'utilisation d'une technique anesthésique balancée (risque relatif = 4,2 (1,1–9,7), $P=0,03$) et surtout avec les myorelaxants (risque relatif = 13,9 (2,1–89,8), $P=0,009$). Le système de cotation de Leventhal présentait une faible sensibilité (22,2 %) et des valeurs prédictives positives (25 %).

Conclusion : *La sévérité de la MG ne permet pas de prédire les besoins de ventilation postopératoire. Une technique anesthésique combinée permet de remplacer l'anesthésie balancée de façon sûre et rentable, car elle fournit des conditions opératoires maximales et entraîne moins d'admissions à l'USI et des séjours hospitaliers plus courts.*

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MYASTHENIA gravis (MG) is a rare autoimmune disease characterized by fluctuating muscle weakness and fatigability due to a reduction in available acetylcholine receptors at the neuromuscular junction.[1] The role of the thymus has been suggested by the presence of tumours and germinal centres in a majority of patients with MG and by the beneficial effects of thymectomy in about 40–90% of patients.[2,3] Besides thymectomy, therapy with anticholinesterase drugs, - providing an increase in acetylcholine - is of partial clinical benefit whereas the use of corticosteroids, immunosuppressive drugs and plasmapheresis often improve the prognosis of those patients resistant to anticholinesterase drugs or with life-threatening symptoms.[4,5]

Clinicians are well aware of the risk of postoperative respiratory failure[6,7] that may result from stress-induced exacerbation of MG (myasthenic crisis), an overdose of anticholinesterases (cholinergic crisis), the residual effects of myorelaxants or other adverse drug interactions (with antibiotics or antiarrhythmics). Therefore, routine postoperative ventilatory support and planned extubation in the intensive care unit (ICU) have been recommended in high-risk patients. To predict the need for postoperative ventilation, Leventhal *et al.* proposed a scoring system which takes into account the duration of MG, the dosage of pyridostigmine, lung functional volumes and the presence of concomitant respiratory diseases.[8]

Various anesthetic approaches have been reported in MG patients.[7,9,10] In our institution, thoracic epidural anesthesia in combination with propofol anesthesia has been routinely performed since 1994. The purpose of this retrospective study was to determine if a combined technique could be safely substituted to balanced anesthesia in MG patients undergoing thymectomy and to question whether the need for postoperative ventilation could be accurately predicted.

Methods

From January 1980 to March 2000, 36 consecutive patients with MG underwent thymectomy and were managed by the same medical team at the University Hospital of Geneva. The medical and nursing charts of patients with MG were reviewed retrospectively. All patients had MG proven by an anticholinesterase test and by electroneuro-myographic assessment. According to the classification by Osserman and Genkins,[11] the clinical severity of MG was graded in five stages (I, ocular signs only; IIA, generalized mild muscle weakness; IIB, generalized moderate weakness and/or bulbar dysfunction; III, acute fulminating presentation and/or respiratory dysfunction; IV, late generalized weakness). Besides routine examinations, preoperative investigations included chest computed tomography scan, lung volume spirometry and detection of various circulating auto-antibodies (anti-acetylcholine receptor, anti-smooth muscle cell, anti-nuclear factor). Patients' preoperative characteristics are summarized in Table I. For each patient, the preoperative risk score was calculated according to Leventhal *et al.*(see appendix).

The operations were performed by three experienced thoracic surgeons either through thoracic incision, transcervical approach (n=5; n=7), or via sternotomy (n=24). An arterial line was inserted in all patients with respiratory symptoms (n=19). Tracheal extubation was performed in the operating room ("early" extubation) or in the intensive care unit (ICU) ("delayed" extubation) when the patient appeared fully responsive and could generate an inspiratory force greater than -20 cm H_2O. The usual dose of pyridostigmine was administered prior to surgery. Pyridostigmine was resumed within six hours after surgery at a lower dose; neostigmine (2.5–5 mg) was given intravenously in those patients who were unable to swallow.

Data were collected concerning anesthetic variables and any perioperative complications. In the immediate postoperative period, difficulties with weaning and the duration of mechanical ventilatory support were evaluated. At regular follow-up visits, neurologists adjusted the medical treatment and assessed the time course of the disease.

TABLE I Demographic, clinical and histological characteristics of 36 patients with myasthenia gravis (n patients, median (range))

Demographic data	
Gender (male/female)	10 /26
Age (yr)	37 (18–66)
Body mass index	23 (17–35)
Osserman staging of myasthenia gravis	
IIA	11
IIB	7
III	16
IV	2
Histology	
Thymoma	12
Hyperplasia	15
Atrophy	9
Preoperative treatment	
Pyridostigmine (n patients)	33
dosage (mg)	180 (40–490)
Prednisone (n patients)	5
dosage (mg)	25 (15–70)
Plasmapheresis (n patients)	16
Disease duration (mo)	12 (1–132)
≥72 mo (n patients)	4
Vital capacity (% predicted value)	92 (60–112)

TABLE II Anesthetic management of 36 patients with myasthenia gravis

	n patients	*Dosage (median, range)*
Balanced anesthesia		
Halothane	12	1.6 (0.5–2.8)%
Enflurane	8	1.4 (0.8–2.0)%
Isoflurane	3	1.3 (0.6–1.5)%
Desflurane	1	2.5 (1.5–4.2)%
Fentanyl	29	2.3 (1.8–4) $mg \cdot kg^{-1}$
Sufentanyl	3	0.12 (0.08–0.15) $\mu g \cdot kg^{-1}$
Alfentanyl	4	46 (35–44) $\mu g \cdot kg^{-1}$
Pancuronium	2	0.03–0.05 $mg \cdot kg^{-1}$
Atracurium	3	0.03–0.04 $mg \cdot kg^{-1}$
Vecuronium	3	0.02–0.05 $mg \cdot kg^{-1}$
Combined anesthesia		
Propofol *iv* $mg \cdot kg^{-1} \cdot hr^{-1}$	12	0.12 (0.07–0.17)
Bupivacaine 0.25%	12	10 (7–12) $ml \cdot hr^{-1}$
Sufentanyl	12	0.07 (0.05–0.09) $\mu g \cdot kg^{-1}$

Data are expressed as median and range or absolute numbers. When appropriate, statistical evaluation was performed using Mann-Whitney *U*-test, Wilcoxon test, power analysis and chi-square analysis (^{2}) with Fisher' exact test. The sensitivity, specificity and predictability of Leventhal's scoring system were also determined.

Results

Over a 21-yr period, thymectomy for MG was performed under two different types of anesthesia (Table II): 1) from 1980 to 1993, a balanced technique included various inhalational agents with small doses of opiates (n=24) and myorelaxants in eight cases; 2) since 1994, *iv* propofol was combined with epidural administration of bupivacaine and sufentanil (n=12).

Successful tracheal extubation was achieved in 28 patients in the operating room ("early" extubation) whereas five patients required three to four hours of ventilatory support and three others remained intubated for eight, 19 and 48 hr after the end of surgery ("delayed" extubation). Patients managed with a combined general and epidural anesthesia were all extubated immediately after surgery (Figure 1) and were electively admitted in the postanesthesia care unit, after balanced anesthesia, a majority (22 of 24) were admitted in the ICU.

There were no differences between the "delayed" and "early" extubation groups with regard to preoperative clinical staging, body mass index, anticholinesterase dosage, duration of the disease, histological diagnosis, lung function, duration of surgery, infusion of intraoperative fluid and surgical technique (Table III).

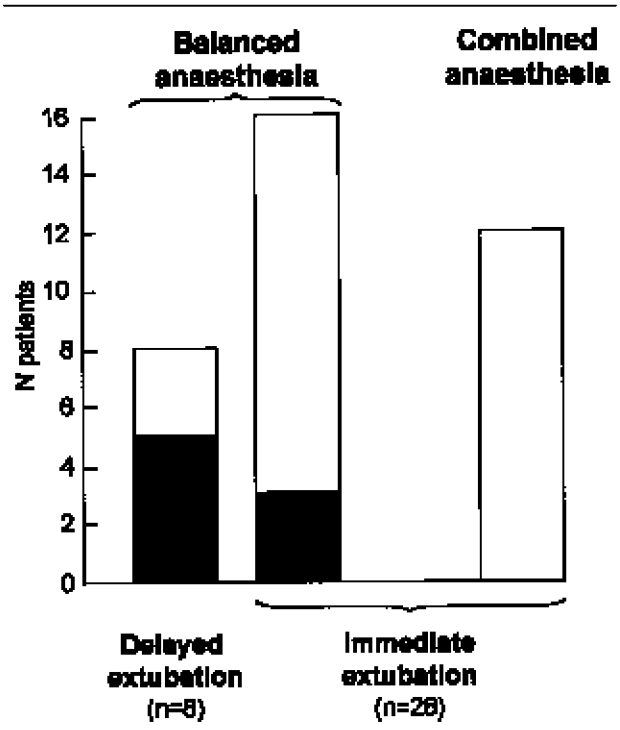

FIGURE 1 Delayed or early extubation after thymectomy under balanced or combined anesthesia, with (■) or without (❑) muscle relaxants.

TABLE III Characteristics of patients with immediate *vs* delayed extubation

	Immediate extubation n=28	*Delayed extubation n=8*
Body mass index ($kg \cdot m^2$)	23 (4)	25 (2)
Clinical stage (Osserman 1 to 4)	2.5 (1–3)	3 (2–4)
Vital capacity (% predicted value)	78 (12)	72 (10)
Dose of pyridostigmine (mg)	201 (128)	188 (117)
Delay from diagnosis to surgery (min)	17 (1–132)	6 (1–19)
Sternotomy / thoracotomy / cervicotomy	19/4/5	5/3/0
Duration of surgery (min)	80 (26)	87 (27)
Intraoperative *iv* fluid (ml)	1739 (735)	1525 (632)
Thymoma / hyperplasia / atrophy	6/12/10	5/2/1

Postoperative ventilatory support was more frequently required when a balanced anesthetic technique was performed (odds ratio=4.2 (1.1–9.7), P=0.03) and particularly in patients who were given myorelaxants (odds ratio=13.9 (2.1–89.8), P=0.009).

No patient required re-intubation for myasthenic or cholinergic crisis. Compared with the "early" extubation group, patients with delayed extubation had a

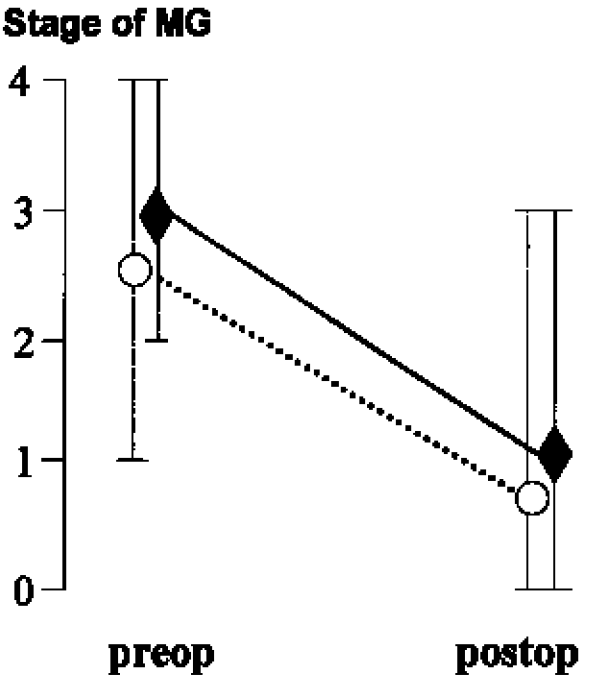

FIGURE 2 Preoperative and postoperative clinical assessment (Osserman staging) in myasthenia gravis patients who had delayed (○) or immediate (◆) postoperative extubation (median and range).

more prolonged hospital stay (median stay=12 days, range (8–28) *vs* five days (4–15), $P < 0.05$) but had similar clinical improvement six months after thymectomy (Figure 2). Bronchopneumonia was diagnosed on the 5th postoperative day in one patient who was ventilated for 19 hr postoperatively.

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.

Discussion

In this retrospective series, eight of 36 patients with MG required short-term postoperative ventilatory support but had similar clinical improvement compared with patients extubated immediately after thymectomy. Neither the severity of MG nor any surgical variable or histological finding were useful to predict difficulties with weaning from mechanical ventilation. Importantly, a combined epidural and general anesthetic technique appeared to facilitate early extubation.

Although determination of any multivariate scoring system is often fraught with methodological errors, current anesthesia textbooks still refer to Leventhal's criteria to predict the need for postoperative ventilatory support in MG.[12,13] The validity of this scoring has been confirmed in a series of 41 patients undergoing thymectomy through transcervical, transsternal and thoracic approach.[14] In contrast, no predictive value was demonstrated when applied only to transcervical thymectomy patients.[15] Likewise, we documented low sensitivity and low positive predictive values in a our series involving three different surgical approaches.

In their original retrospective study, Leventhal *et al.* applied stepwise multivariate discriminant analysis to 21 preoperative factors among 24 patients.[8] Knowing that the number of variables examined should be no more than 10% of the number of outcomes (postoperative ventilation),[16] data on more than 600 patients should have been collected or/and the number of potential predictors should have been markedly restricted (e.g., four factors examined in 120 patients) to establish a stable and accurate scoring system. Hence, in our small series, we only performed a *uni*variate analysis to detect possible risk factors; a multicentre study or pooling of several previous investigations, would have been necessary to apply *multi*variate analysis and to detect the independent predictors of postoperative respiratory insufficiency.

Our data suggest that the ability to sustain spontaneous ventilation after thymectomy appears to be less dependent on the clinical severity of MG evaluated by Leventhal'scoring than on the recent development of perioperative medical care. The combination of several factors likely contributed to facilitate postoperative extubation over the last seven years. It is possible that preoperative muscular atrophy was attenuated by using lower doses of corticosteroids and that neuromuscular function was further optimized by using other immunosuppressive drugs and plasmapheresis which eliminates circulating auto-antibodies against acetycholine receptors.[4,17] In addition, the risk of respiratory failure may have been decreased by using less invasive surgical approaches (cervicotomy, partial sternotomy or mini-thoracotomy), avoiding myorelaxants and long acting anesthetic agents and by providing adequate postoperative analgesia.[15,18,19]

In our institution, - from 1980 to 1993 -, non-standardized balanced anesthesia protocols were applied and included various inhaled agents, small doses of opiates and, in some cases, muscle relaxants. Postoperative pain was poorly controlled due to fear of respiratory depression and the need for ventilatory support was more frequent when muscle relaxants were given intraoperatively. Since 1994, we have elected to perform thoracic epidural anesthesia in combination with general anesthesia in all patients undergoing thymectomy via

a sternal or thoracic approach. Using a similar anesthetic technique, Suwanchida *et al.*[20] confirmed the higher incidence of early extubation compared with balanced anesthesia (78 *vs* 29%). Not surprisingly, emergence from anesthesia was facilitated by providing maximal analgesia, minimizing the interactions with opiates and muscle relaxants and by rapid elimination of propofol.[21] The inherent sedative properties of neuraxial blockade has been shown to reduce the requirements for general anesthetic agents by approximately 50%[22] and the addition of opiates to epidural bupivacaine further enhances such synergistic effect.[23]

Nondepolarizing muscle relaxants were avoided and adequate surgical conditions were provided by *iv* propofol anesthesia. Good intubating conditions with acceptable jaw mobility and vocal cord relaxation can be obtained under propofol anesthesia without using muscle relaxants.[24] Experimental data suggest that propofol attenuates skeletal muscle contractions by presynaptic inhibition of acetylcholine release and by slowing of calcium shifts through the muscle membrane.[25]

The decrease in available acetycholine receptors explains the resistance of MG patients to succinylcholine and the increased sensitivity to nondepolarizing relaxants and inhaled anesthetics which is associated with longer duration of the disease, higher preoperative pyridostigmine dose and elevated level of circulating antibodies.[26] Although it seems prudent to avoid muscle relaxants, several recent studies have reported early extubation when muscle relaxants (vecuronium, atracurium, cisatracurium) were used in association with short-acting inhaled anesthetics (desflurane, sevoflurane) and *iv* opiates.[26–30] In such cases, neuromuscular monitoring is particularly helpful to titrate the administration of muscle relaxants but also as a diagnostic tool: a marked decrement in the preanesthetic muscular response to repetitive stimulation (T4/T1 <0.9) identifies patients who require less than 30% of the usual atracurium dose to achieve 95% neuromuscular blockade (ED_{95}).[29]

Although this report is subjected to the limitations of a retrospective study including missing data, bias in investigator assessment as well as poor control of preoperative, surgical and anesthetic variables, it provides the opportunity to gather information on a large number of patients with a rare disorder and to assess the clinical impact of a new anesthetic approach on patients' outcome in a single medical centre. Randomized controlled trials are not always possible for ethical considerations, clinical judgement and unwillingness on the part of the investigators or patients.[31] Therefore, we must also rely on observational studies to identify risk factors for morbidity/mortality and to evaluate new healthcare interventions.

In an era of cost-containment, it is significant that provision of medical care is aimed at reducing the length of hospital stay, particularly in ICUs, while preserving or improving outcome and quality of life. Standardization of anesthesia procedures has been demonstrated to reduce the risk of human errors and to decrease medical charges. In our study, the shift in management of MG patients from balanced anesthesia (with various agents) to a standardized combined technique (without muscle relaxants) provided optimal operating conditions, improved patient comfort following transsternal and thoracic incision, avoided the need for postoperative ventilatory support and resulted in fewer admissions in ICU and shorter duration of hospital stay.

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APPENDIX

Predictors for postoperative need of mechanical ventilation (based on reference #8)
Duration of myasthenia gravis 72 mo: 12 points
History of chronic respiratory disease : 10 points
Pyridostigmine dosage >750 mg/day: 8 points
Vital capacity <2.9 L: 4 points