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Original Article

Preoperative risk factors for prolonged postoperative ventilation following thymectomy in myasthenia gravis

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Abstract: Adequate preoperative evaluation and preparation for surgery are required to prevent prolonged mechanical ventilation after thymectomy, and facilitate the recovery of patients with myasthenia gravis (MG). The objective of this study was to identify the preoperative risk factors for extubation failure after thymectomy in patients with MG. Methods: A retrospective study was conducted on 61 patients with MG who underwent extended thymectomy. Several factors were evaluated including patients' demographic data, preoperative medical therapies, medical history, and comorbidities. Multivariate logistic regression analysis was used to identify the predictors of late extubation after thymectomy for MG. Results: Fourteen patients (22.95%) required breathing support after anesthesia or endotracheal re-intubation within 48 h. Univariate analysis illustrated that the quantitative MG (QMG) grade (odds ratio [OR] = 1.368, P = 0.000), preoperative muscle strength (OR = 0.279, P = 0.000), use of pyridostigmine (OR = 1.011, P = 0.024) and prednisone (OR = 1.059, P = 0.022), preoperative lung function (OR = 4.875, P = 0.016), low preoperative cholinesterase levels (OR = 0.999, P = 0.014), impaired preoperative swallowing muscle activity (OR = 7.619, P = 0.003), and positivity for acetylcholine receptor antibodies (OR = 14.143, P = 0.001) were significant predictors of prolonged postoperative intubation. Multivariate logistic regression analysis revealed that the QMG score (OR = 3.408, P = 0.000) and Myasthenia Gravis Foundation of America (MGFA) classification (OR = 28.683, P = 0.002) were independent risk factors for prolonged postoperative intubation. Conclusion: The preoperative MGFA clinical classification and QMG score were independent risk factors for prolonged postoperative intubation in patients with MG.

Keywords: Myasthenia gravis, thymectomy, airway extubation, risk factors

Introduction

Myasthenia gravis (MG) is an autoimmune neuromuscular disease that leads to fluctuant muscle weakness and fatigue caused by circulating antibodies against postsynaptic acetylcholine receptors (AchRs). Thymoma and thymus hyperplasia are observed in 10-15% and more than 60%, respectively, of patients affected by MG [1]. In these patients, thymectomy is considered a viable surgical alternative, as it can improve or cure the disease in 54-94% (in case of thymoma) or 21-42% (in the case of thymus hyperplasia) of patients [1]. However, postoperative crisis remains a major challenge that can necessitate postoperative mechanical ventilatory support [2]. For these reasons, routine postoperative ventilatory assistance and planned extubation in the intensive care unit (ICU) are recommended for high-risk patients. Moreover, extubation failure is relatively common in patients with myasthenic crisis, who sometimes require re-intubation owing to muscular weakness. In the elderly, pulmonary complications and atelectasis are strong predictors of extubation failure [3, 4]. Leventhal et al. identified four factors predicting a higher risk of the need for postoperative ventilatory support, i.e., duration of myasthenia, respiratory-associated disease, preoperative pyridostigmine dosage, and vital capacity [5]. Despite these data, predicting the requirement for postoperative ventilatory support remains difficult in patients with MG because of the development of anesthesia protocols, muscle relaxants, and neuromuscular monitoring. Furthermore, the ideal timing for extubation and factors influencing the success of extubation have not been well established. Nonetheless, prolonged postoperative mechanical ventilation increases the occurrence of ventilation-associated complications (ventilator-associated pneumonia and atelectasis), the number of patients admitted to the ICU, and the length of hospital stay [2].

Therefore, we conducted this retrospective study to identify preoperative factors associated with prolonged postoperative mechanical ventilation and extubation failure in a series of patients with MG undergoing thymectomy.

Materials and methods

Subjects

We retrospectively analyzed all patients with MG who underwent extended thymectomy between January 2007 and February 2012 at Yijishan Hospital of Wannan Medical College. The study was registered at ww.chictr.org (ChiCTR-OCC-14004533). We included all patients with a diagnosis of MG who were older than 18 years of age and who were undergoing elective extended thymectomy, possibly while in remission.

Anesthesia protocol

General anesthesia was conducted according to a local protocol. In particular, preoperative respiratory tests were conducted in addition to general evaluations needed for general anesthesia. Of note, to avoid interactions with other drugs (such as ester-type local anesthetics and aminoglycoside antibiotics) used during anesthesia, anticholinesterase therapy was withheld on the morning of surgery.

During the surgery, heart rate, electrocardiography, noninvasive blood pressure, pulse arterial oxygen saturation, and neuromuscular function (TOF mode) were continuously monitored when neuromuscular blocking agents were used. Tracheal extubation was attempted for all patients in the operating room. At the end of the surgery, extubation was performed under the following conditions: 1) T_4/T_1 of TOF monitoring was 0.9 or higher, 2) the patient was responsive and able to generate a negative inspiratory pressure of more than -20 cmH_2O [6], and 3) after a successful spontaneous breathing trial with a T-piece for 30 min [7, 8].

If the criteria were not fulfilled in the postoperative period, patients underwent a progressive weaning protocol in the ICU. Patients were maintained with endotracheal intubation and ventilation using the synchronized intermittent mandatory ventilation mode in the ICU, and the amount of respiratory support was gradually reduced until extubation after reaching the target parameters. All patients were monitored for at least 24 h in the ICU for safety. In the case of one of the following conditions, noninvasive ventilation was attempted to avoid re-intubation: 1) severe dyspnea (respiratory rate > 30 breaths/min), 2) arterial partial pressure to inspired fraction of oxygen ratio of less than 200 mmHg, and 3) respiratory acidosis (pH < 7.30 with an arterial partial pressure of carbon dioxide > 50 mmHg). Re-intubation was required in the presence of two of the previous criteria, noninvasive ventilation attempt failure, or neurological status alteration (loss of 2 or more points on the Glasgow Coma Scale [GCS] or GCS < 10).

Patients were classified in two groups: 1) "difficult to extubate" (group I), i.e., requiring weaning in the ICU or re-intubation within 48 h; and 2) "easy to extubate" (group II), i.e., those who underwent extubation in the operating room.

Data collection

Data were collected for the following variables before surgery: patients' demographics; preoperative medical therapies (including prednisone and/or anticholinesterase therapy); medical history and comorbidities; and results of chest X-ray and/or computed tomography (CT), pulmonary function tests, and preoperative blood tests (including AChR antibody status). Muscle strength was evaluated in five different classes according the diagnostic score of the nervous system. Normal lung function was defined using the breath-holding test (< 20 s) [9]. Dysfunction of swallowing muscle activity was assessed by asking the participants to swallow one-half cup of water (severe cough/choking indicated dysfunction) [10]. Comorbidities, such as chronic lung diseases and chronic cardiovascular diseases (including hypertension, coronary heart disease, and heart failure), were also recorded.

In 2000, the Myasthenia Gravis Foundation of America (MGFA) recommended that the quantitative MG (QMG) score should be used in com-

Table 1. Univariate analysis of patients with myasthenia gravis with and without prolonged postoperative extubation

Variables	Group I (n = 14)	Group II (n = 47)	*P* value	OR	95% CI
Gender (n)			0.795	1.173	0.352-3.910
Male	6	22			
Female	8	25			
Age (years)	40.3 + 11.0	33.8 + 15.8	0.160	1.030	0.988-1.075
MGFA clinical classification			0.015*	1.581	0.966-2.587
I	3	30			
IIa + IIb	10	14			
IIIa + IIIb + IV	1	3			
QMG grade	9.64 + 2.79	4.02 + 4.11	0.000*	1.368	1.149-1.628
Muscle strength			0.000*	0.279	0.131-0.593
Level 2	1	2			
Level 3	8	3			
Level 4	3	12			
Level 5	2	30			
Prednisone (mg)	13.2 + 13.1	5.3 + 10.5	0.023*	1.059	1.008-1.112
Pyridostigmine (mg)	175.7 + 36.9	110.4 + 93.6	0.000*	1.011	1.001-1.020
Smoking history			0.650	1.324	0.393-4.457
With	6	17			
Without	8	30			
History of chronic lung diseases			0.549	2.291	0.473-11.098
With	3	5			
Without	11	42			
History of chronic cardiovascular diseases			0.440	2.286	0.558-9.366
With	4	7			
Without	10	40			
Lung function			0.031*	4.875	1.336-17.793
Normal	7	39			
Abnormal	7	8			
ALT (U/L)	33.4 + 19.2	28.9 + 20.7	0.470	1.010	0.983-1.039
ALB (g/L)	45.0 + 9.9	44.4 + 4.2	0.814	1.018	0.923-1.123
Cr (μmol/L)	64.4 + 28.3	63.6 + 20.0	0.916	1.011	0.974-1.029
CHE (mmol/L)	3235.2 + 832.0	3959.6 + 936.0	0.012*	0.999	0.998-1.000
K^+ (mmol/L)	4.23 + 0.26	4.19 + 0.36	0.677	1.477	0.244-8.960
Hb (g/L)	125.7 + 14.9	127.0 + 14.7	0.772	0.994	0.953-1.036
AchR antibody			0.000*	14.143	2.793-71.625
(+)	12	14			
(-)	2	33			
Impaired swallow muscle activity			0.004*	7.619	2.018-28.768
With	8	7			
Without	6	40			

*P < 0.05, group I vs. group II. Abbreviations: OR, odds ratio; CI, confidence interval; MGFA, Myasthenia Gravis Foundation of America; QMG, quantitative myasthenia gravis; ALT, alanine transferase, ALB, albumin, Cr, creatinine; CHE, cholinesterase; Hb, hemoglobin; AchR, acetylcholine receptor.

bination with the MGFA clinical classification and the postintervention status [11]. Thus, in this study, a detailed investigation was performed, and clinical status was assessed according to the MGFA clinical classification scheme and QMG scoring system.

Table 2. Multivariate prognostic factor analyses of patients with prolonged postoperative extubation using logistic regression analyses

Variables	Variable risk	SE	Wald	*P* value	OR value	95% CI
QMG score	1.226	0.342	12.856	0.000	3.408	1.744-6.663
MGFA clinical classification	3.356	1.101	9.289	0.002	28.683	3.313-248.299

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; QMG, quantitative myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America.

Statistical analysis

All continuous data are expressed as the mean ± standard deviation. Student's *t*-test was performed as appropriate for comparisons of continuous variables. Categorical variables were analyzed using χ^2 tests as appropriate in contingency tables. Furthermore, related variables were used for the determination of statistically significant predictors of prolonged extubation. Logistic regression analysis along with a stepwise procedure was applied for univariate and multivariate analyses to confirm the impact of the aforementioned factors on clinical outcomes. All tests were two-sided, and differences with *P* values of less than 0.05 were considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, version 13.0, Chicago, IL, USA).

Results

Patients

A total of 61 patients (33 women and 28 men; age, 18-66 years) with MG who were scheduled to receive general anesthesia requiring tracheal intubation for elective surgery were included in this analysis. The duration of symptoms prior to surgery ranged from 1 month to 2 years. The operative time was 60-122 min. No surgical complications, including hemorrhage, re-operation, pneumothorax, hydrothorax, or chylothorax, were observed in any patient.

Sixty-one patients underwent extended thymectomy. Accordingly, patients were divided into two groups: group I included 14 patients with prolonged postoperative mechanical ventilation and group II included the remaining 47 patients who did not require prolonged postoperative mechanical ventilation. Within group I, six patients experienced prolonged postoperative mechanical ventilation for less than 24 h. Prolonged postoperative mechanical ventilation exceeding 24 h or repeated endotracheal incubation was required in eight patients, and postoperative myasthenic crisis occurred in two patients. The rate of prolonged postoperative mechanical ventilation was 22.95%.

Characteristics of patients with MG with or without prolonged postoperative mechanical ventilation

The difference in the MGFA clinical classification was significant between the two groups. The rate of prolonged extubation was significantly higher in patients with a high QMG grade, low grade of preoperative muscle strength, abnormal preoperative lung function, low preoperative levels of cholinesterase (CHE), positivity for AchR antibodies, impaired preoperative swallowing muscle activity, and preoperative use of prednisone and/or CHE inhibitors than in patients without these conditions (**Table 1**).

Univariate and multivariate analyses

Significant univariate predictors of prolonged postoperative mechanical ventilation were the QMG grade (odds ratio [OR] = 1.368, *P* = 0.000), preoperative muscle strength (OR = 0.279, *P* = 0.000), use of pyridostigmine (OR = 1.011, *P* = 0.024) and prednisone (OR = 1.059, *P* = 0.022), preoperative lung function (OR = 4.875, *P* = 0.016), low preoperative CHE levels (OR = 0.999, *P* = 0.014), impaired preoperative swallowing muscle activity (OR = 7.619, *P* = 0.003), and positivity for AchR antibodies (OR = 14.143, *P* = 0.001) (**Table 1**). Multivariate logistic regression analyses illustrated that the QMG grade (OR = 3.408, *P* = 0.000) and MGFA clinical classification (OR = 28.683, *P* = 0.002) were independent predictors of prolonged postoperative mechanical ventilation (**Table 2**).

Discussion

Following thymectomy, patients with MG may require postoperative ventilation because of respiratory muscular weakness; however, prolonged postoperative mechanical ventilation could induce postoperative respiratory complications [12]. In this study, we found that breathing support or prolonged postoperative intubation was common in patients with MG (22.95% of patients in this series), and two of the crises were complicated. Patients who required prolonged postoperative mechanical ventilation had much longer ICU and hospital stays. However, previously proposed guidelines failed to predict extubation outcomes in several types of patients. Thus, it is crucial to identify the possible preoperative predictors of prolonged postoperative mechanical ventilation in the ICU.

In this study, most patients needed postoperative ventilation if they exhibited impaired preoperative muscle strength, lung function, and swallowing muscle activity. Varelas et al. [13] proposed that extubation can be attempted when patients are breathing comfortably, are not fatigued, and have a mouth inspiratory pressure of -20 cmH_2O or better in conjunction with normal blood gases. Hence, these local practice guidelines rely substantially on the results of bedside pulmonary function parameters. However, patients with MG and significant residual bulbar weakness requiring prolonged intubation are at risk of significant upper airway collapse when the stenting effect of the endotracheal tube is no longer present after extubation [14]. Conversely, patients with MG and significant facial weakness may exhibit poor pulmonary function results, even after their respiratory muscles have recovered adequate strength. Therefore, we considered it important to specifically assess the role of bedside pulmonary function parameters in predicting the outcome of extubation. Younger et al. [15] found that expiratory weakness was the main determinant of the need for postoperative supported ventilation in myasthenic patients. The expiratory muscles are needed to clear secretions, and they may be weaker than the inspiratory muscles in many patients [16]. Additionally, postoperative myasthenic crisis is frequently caused by lung function impairment resulting from infection of the respiratory tract [17]. Therefore, aggressive respiratory treatment may prevent these complications and reduce the frequency of failed extubation.

Surprisingly, pyridostigmine and prednisone doses, low preoperative CHE levels, and AchR antibody positivity proved to have the greatest value in predicting the need for ventilatory support, suggesting that patients with MG may be more susceptible to stressful situations, such as surgical intervention. The results were consistent with previous studies [18, 19]. Steroid use after thymectomy has been reported to be a predictor of poor outcomes, as steroids are used in patients with poor responses to thymectomy [18]. Thus, patients with good responses to thymectomy could be administered reduced levels of prednisolone. In our study, patients exhibiting positivity for AchR antibodies were sensitive to delayed extubation. Loss of these receptors leads to defects in neuromuscular transmission with muscle weakness and fatigue [20]. AChR antibodies are absent in approximately 15% of patients with MG.

In a multivariate analysis, two risk factors present at baseline were significantly and independently associated with prolonged intubation, consistent with previous reports: 1) the preoperative MGFA clinical classification and 2) QMG score [18, 21]. Many studies illustrated that patients with lower MG stages display better responses to thymectomy and high remission rates. An analysis by Chu et al. [2] demonstrated that the Osserman stage (IIb + IIIb + IV), thymoma, and major postoperative complications are independent predictors of postoperative myasthenic crisis in patients with MG who underwent thymectomy. However, high QMG scores do not correspond with high MGFA clinical classifications. A task force of the Medical Scientific Advisory Board of the MGFA recommended possible weighting of individual items within the QMG score as well as evaluation of more objective methods of measuring muscle strength [10].

Surprisingly, some traditionally used clinical criteria for evaluating patients with MG were found to be unimportant in our analysis. Gender, age, and histories of chronic lung and cardiovascular diseases all failed to add to the predictive ability of the discriminant function. This argument was supported by the older age of the patients in the extubation failure and reintubation groups [4]. Age at the time of surgery has been reported as a potential factor affecting clinical outcomes. Indeed, some authors observed that patients younger than 50 years have better clinical outcomes than elderly patients [22]. Older age and the development of pulmonary complications during mechanical ventilation have been reported to increase the risk of extubation failure [3]. This difference could be explained by several observations. First, the mean age reported in the published data ranges from 53.8 to 62 years, compared with 35.3 years in our patients. In addition, in the study by Leventhal et al., the researchers found that a history of respiratory disease was a risk factor based on data from only three patients (of 24 total patients) [5]. Another important factor that should be considered is that the preoperative optimization of the patients' conditions may have improved over the past 35 years.

One limitation of this study was that several preoperative variables, including preoperative blood gas values and cardiopulmonary function test data, could not be evaluated adequately because the data were missing for many patients. Further, we did not have patients with all clinical events of myasthenia. It is possible that some factors that were not found to be significant in this study may become significantly predictive if more patients are included in the analysis. However, recruiting a larger sample would be difficult because of the rarity of this disease. In addition, our analysis highlighted the preoperative factors that appear most important in determining postoperative ventilatory capabilities because the preoperative variables could be particularly useful and easily applied clinically. Additionally, intra-operative management data, such as the administration of sedative agents and muscle relaxants, were not presented in the study, which may affect respiratory function in general. However, because of the development of sedative agents and muscle relaxants, data have illustrated that a standardized combined anesthetic technique provides optimal operating conditions, avoiding the need for postoperative ventilatory support and resulting in fewer admissions to the ICU and shorter hospital stays [23]. Further prospective studies of these risk factors, including operation and anesthesia, are needed for complete evaluations; future studies should be carefully designed to address these issues.

In conclusion, various factors have been suggested to influence extubation after thymectomy in myasthenic patients. Among these, preoperative MGFA clinical classifications and QMG scores appear to be the most important potential predictors of prolonged postoperative extubation. Therefore, more attention should be paid to patients with high QMG scores or high MGFA clinical classifications to reduce the rate of delayed extubation and improve the prognosis of patients with MG.

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Disclosure of conflict of interest

None.

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