ORIGINAL CONTRIBUTION

Predictors of Extubation Failure in Myasthenic Crisis

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Background: The ideal timing for extubation of patients with myasthenic crisis (MC) and the factors that influence extubation outcome are not well established.

Objectives: To assess the risk of extubation failure in MC and to identify predictors of extubation failure.

Design: We reviewed consecutive episodes of MC treated with endotracheal intubation from January 1, 1987, through December 31, 2006.

Setting: Mayo Clinic.

Patients: Forty patients with 46 episodes of MC underwent endotracheal intubation and mechanical ventilation.

Main Outcome Measures: The main outcome measures were extubation failure and reintubation. *Extubation failure* was defined as reintubation, tracheostomy, or death while intubated. Reintubation was also analyzed as a separate end point. Univariate logistic regression was used to identify predictors of extubation failure and reintubation.

Results: Of the 46 episodes of MC, extubation failure occurred in 20 (44%), including 9 of 35 episodes (26%) of reintubation. Male sex, history of previous crisis, atelectasis, and intubation for more than 10 days were associated with extubation failure. Lower pH and lower forced vital capacity on the time of extubation, atelectasis, and bilevel intermittent positive airway pressure use after extubation predicted the need for reintubation. Atelectasis showed the strongest association with both end points. Extubation failure and reintubation were associated with significant prolongation in intensive care unit and hospital length of stay.

Conclusions: Extubation failure is relatively common in patients with MC. Atelectasis is the strongest predictor of this complication.

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MYASTHENIC CRISIS (MC) is defined by the development of neuromuscular respiratory failure from myasthenia gravis that requires mechanical ventilation or endotracheal intubation for airway protection.[1] Approximately 8% to 27% of patients with myasthenia gravis experience MC,[2] and the mortality of patients with MC has decreased from more than 40% in the early 1960s to approximately 5% in the 1970s.[3] The improved prognosis can be attributed to improved respiratory care during crisis, including introduction of intensive care units (ICUs), substitution of endotracheal intubation for tracheostomy, and improvements in monitoring, tracheal toilet, and antibiotics.

No consensus has been reached regarding when to extubate patients treated for MC. One study[4] found a considerable variation in time on the ventilator, with 25% of patients extubated by day 7, 50% by day 13, and 75% by day 31. Clinical experience has taught us that weaning patients from the ventilator after MC treatment is often difficult. In some patients, weaning from mechanical ventilation is complicated by fluctuating degrees of weakness and development of pulmonary complications, but the causes of weaning and extubation failure remain unknown in other cases. Physical examination and bedside respiratory parameters are typically used to decide when to proceed with extubation.[4,5] Bilevel intermittent positive airway pressure (BiPAP) may be helpful for avoiding reintubation in myasthenic patients with respiratory insufficiency after extubation,[6] but, to our knowledge, the value of BiPAP for this indication has not been formally evaluated.

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The published data are limited on predictors of extubation failure in patients with MC. Older age and development of pulmonary complications during mechanical ventilation were reported to increase the risk of extubation failure in 1 study.[7] Patients who experienced extubation failure had much longer ICU and hospital stays.[7] The objective of this study was to identify the predictors of extubation failure in patients with MC.

METHODS

This study was approved by the Mayo Clinic institutional review board. We retrospectively identified patients with MC treated at Mayo Clinic from January 1, 1987, through December 31, 2006; these patients underwent endotracheal intubation and mechanical ventilation. Postthymectomy patients, patients with Lambert-Eaton syndrome, patients with congenital myasthenia, and those intubated for cardiac failure or pulmonary disease were excluded from the study. All patients had severe generalized and bulbar weakness and were intubated for neuromuscular respiratory failure (grade V on the Myasthenia Gravis Foundation of America clinical grading scale).

A clinical diagnosis of myasthenia gravis was confirmed in all patients by 1 or more of the following investigations: repetitive nerve stimulation, positive acetylcholine receptor (AChR) antibodies, and single-fiber electromyographic testing. The general criteria for intubation were vital capacity of less than 15 to 20 mL/kg, peak inspiratory pressure lower than −40 cm H_2O, peak expiratory force of less than 40 cm H_2O, and evidence of respiratory muscle fatigue, hypercapnia, or hypoxia. These parameters were used as guidelines, but the actual timing of initiation of intubation was decided by the emergency department staff or intensivists in the ICU based on their clinical judgment.

We collected patient demographic information, including age, sex, weight, time from diagnosis to present crisis, history of MC, history of thymoma, treatment on admission, other medical history, AChR antibody status, and trigger factors (infection, change of medications, and surgery). Baseline, preintubation, and postextubation bedside pulmonary function test (PFT) results, including forced vital capacity (FVC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP), and arterial blood gas (ABG) measurements were recorded. Bedside PFTs were performed using a scubalike device that reduced air leakage.[8] Immunotherapies administered and presence of respiratory complications (atelectasis and pneumonia) or other systemic complications were recorded. Diagnosis of atelectasis required radiologic changes consistent with lobar or segmental collapse. Diagnosis of pneumonia was defined by the presence of fever, positive culture results of respiratory secretions, and radiologic infiltrate or consolidation. Use of T-piece trials during weaning, duration of intubation, and use of BiPAP after extubation were noted.

We considered 2 end points in this study: extubation failure and reintubation. *Extubation failure* was defined as requirement for reintubation, tracheostomy during the same admission, or death while intubated. Reasons for reintubation were subcategorized as upper airway obstruction or respiratory fatigue based on the clinical impression of the treating physician. Lengths of stay in the ICU and hospital were calculated to determine the effect of extubation failure on these measures.

Descriptive summary statistics were reported. Comparisons between the groups of interest were made using the χ^2 test, Fisher exact test, or Wilcoxon rank sum test, as appropriate. To identify the predictors of extubation failure and reintubation, further analysis was performed using univariate logistic regression. All tests were 2-sided, and $P<.05$ was considered statistically significant. Statistical analyses were performed using a commercially available software program (SAS, version 8.0; SAS Institute Inc, Cary, North Carolina).

RESULTS

We identified 46 episodes of MC in 40 patients treated with endotracheal intubation and mechanical ventilation. There were 9 episodes of reintubation (including 4 patients who required tracheostomy after reintubation), 7 episodes that proceeded to tracheostomy without attempted extubation, 11 total tracheostomies, and 4 patients who died while intubated. Thus, the end point of extubation failure was reached in 20 episodes (44%), extubation was not possible in 15 episodes (33%), and reintubation occurred in 9 of 35 episodes (26%) in which extubation was attempted. All episodes of reintubation occurred within the same ICU admission and within 72 hours of extubation.

The median age of patients in our study population was 64.5 years (range, 25-90 years), and the female to male ratio was 1.3:1. History of thymoma was present in 22 patients (48%), median disease duration was 4.5 years (range, 1 month to 43 years), 17 patients (37%) had a previous crisis, and 38 patients (83%) had AChR antibodies. (Percentages are based on 46 episodes.) Bulbar weakness was uniformly present. The most common trigger factor for MC was change in medications (46%), followed by infections (38%) and surgery (14%). The medical treatment during the crisis period included plasma exchange in 29 episodes (63%), intravenous steroids in 11 episodes (24%), and intravenous immunoglobulin in 6 episodes (13%). Mean ventilation duration (including time using BiPAP) was 12.3 days (range, 3-60 days); 12 episodes (26%) required intubation for more than 7 days, and 7 episodes (15%) required intubation for more than 10 days. T-piece trials were used in 12 episodes (in 34% of 35 patients) before extubation. BiPAP was used in 7 episodes (15%) after extubation. The main medical complications were atelectasis in 16 of 44 cases (36%) and pneumonia in 23 of 45 cases (51%).

The results of our analysis of predictors of extubation failure are given in **Table 1**. Male sex, previous crisis, atelectasis, and intubation for more than 10 days were associated with failure to extubate the patient. When we focused the analysis on patients who required reintubation (thus excluding those who underwent tracheostomy or died without an extubation attempt), we identified that lower pH and lower FVC on extubation, atelectasis, and BiPAP use after extubation predicted the need for reintubation (**Table 2**). Younger patients tended to have a greater risk of requiring reintubation. The chances of necessitating reintubation were not significantly affected by prolonged duration of intubation and were not predicted by the maximal inspiratory and expiratory pressures.

Reintubation was associated with longer ICU length of stay (median, 21.0 vs 6.5 days; $P<.001$) and longer hospital stay (median, 42.0 vs 14.5 days; $P=.002$) vs patients who underwent successful extubation. Similar sig-

Table 1. Comparison of Episodes of Myasthenic Crisis With Successful Extubation vs Failed Extubation

Variable	Extubation Failure (n=20)[a]	Extubation Success (n=26)	*P* Value
Age, mean (range), y	62 (30-84)	64.2 (25-90)	.73
Male sex, %	60	31	.05
Duration of crisis, mean (range), y	7.5 (0.08-30)	8.4 (0.08-38)	.67
Previous crisis, %	61	25	.02
Thymoma, %	58	42	.30
AChR antibodies, %	89	88	.93
PE, %	60	65	.71
Intravenous steroids, %	30	19	.40
IVIG, %	10	15	.59
Physiologic parameters on extubation, mean (range)			
pH	7.44 (7.29 to 7.58)	7.46 (7.40 to 7.52)	.77
Pco_2, mm Hg	40.8 (33 to 54)	39.1 (28 to 48)	.81
Hco_3, mmol/L	27.3 (25 to 32)	26.7 (21 to 33)	.63
Po_2, mm Hg	103.7 (56 to 165)	100.6 (54 to 157)	.96
Sao_2, %	95.4 (92 to 98)	96.3 (88 to 98)	.46
FVC, mL/kg	15.6 (7 to 22)	19.4 (8 to 39)	.32
MIP, cm H_2O	–45.7 (–92 to –20)	–55.5 (–100 to –20)	.43
MEP, cm H_2O	40.7 (22 to 60)	53.5 (25 to 80)	.14
BiPAP use after extubation, %	23	13	.68
Atelectasis, %	66	18	.02
Pneumonia, %	61	42	.35
Intubation >7 d, %	40	15	.08
Intubation >10 d, %	30	4	.04

Abbreviations: AChR, acetylcholine receptor; BiPAP, bilevel intermittent positive airway pressure; FVC, forced vital capacity; Hco_3, serum bicarbonate; IVIG, intravenous immunoglobulin; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; PE, plasma exchange; Sao_2, arterial oxygen saturation.
[a] Extubation failure indicates the requirement for reintubation or tracheostomy during the same admission or death while intubated.

Table 2. Comparison of Episodes of Myasthenic Crisis With Successful Extubation vs Episodes That Required Reintubation

Variable	Reintubation (n=9)	No Reintubation (n=26)	*P* Value
Age, mean (range), y	53.8 (30-68)	64.2 (25-90)	.06
Male sex, %	44	31	.45
Previous crisis, %	25	25	>.99
AChR antibodies, %	100	88	.54
Treatment, %			
PE	56	65	.70
IVIG	11	15	>.99
Steroids	44	19	.19
Complications, %			
Atelectasis	100	18	.01
Pneumonia	71	42	.38
Intubation >7 d	22	15	.64
Intubation >10 d	22	4	.16
Physiologic parameters on extubation			
pH, mean (range)	7.39 (7.29-7.52)	7.46 (7.40-7.52)	.01
T-piece use, %	11	31	.39
BiPAP use after extubation, %	50	13	.05

Abbreviations: See Table 1.

nificant associations were found with the end point of extubation failure ($P=.002$ for ICU and $P=.006$ for hospital length of stay).

COMMENT

In this study, we found that reintubation is common in patients with MC (required after 26% of extubations), and one-third of crises were complicated by reintubation or the inability to extubate. Atelectasis and lower pH and FVC on extubation were the main predictors of reintubation. Men with a history of MC who necessitated ventilation for more than 10 days were more likely to have extubation fail or to require tracheostomy. Patients who required reintubation had much longer ICU and hospital stays.

We chose 2 different end points because we considered both clinically relevant. The combined end point of extubation failure included patients reintubated and those who could not be extubated because of the poor evolution of their respiratory status (they required tracheostomy or died). Thus, this end point identifies crises with refractory ventilatory failure. Meanwhile, using the end point of reintubation allowed us to analyze predictors that could be used in practice to guide the timing of extubation. The complementary value of these 2 end points is best illustrated by their different association with age. Reintubation tended to be more common in younger patients, but this finding probably resulted from a more aggressive approach toward intubation and a greater proclivity to attempt intubation in younger patients before deciding to perform a tracheostomy. This argument is supported by the older age of the patients in the extubation failure group compared with the reintubation group (mean age, 62.0 vs 53.8 years) because the difference was driven by the older age of patients who underwent tracheostomy without a preceding extubation attempt.

General guidelines to determine the timing of extubation in patients with MC have been proposed. Mayer[9] suggested that weaning trials should be considered when there is clear evidence of improved muscle strength (MIP >-20 cm H_2O, MEP >40 cm H_2O, and FVC >10 mL/kg). Varelas et al[5] proposed that extubation can be attempted when patients are breathing comfortably, do not become fatigued, have an FVC of at least 15 mL/kg, and have an MIP of -20 cm H_2O or better in conjunction with normal blood gases. Hence, these local practice guidelines rely substantially on the results of bedside PFTs. However, intubated patients with MC with significant residual bulbar weakness may perform well on PFTs but are at a risk of significant upper airway collapse when the stenting effect of the endotracheal tube is no longer present after extubation.[10] Conversely, patients with MC with significant facial weakness may demonstrate poor PFT results because of technical reasons, even after their respiratory muscles have recovered adequate strength. Therefore, we thought it was important to specifically assess the role of bedside pulmonary function parameters in predicting the outcome of extubation.

Our results indicate that lower pH and lower FVC at extubation are associated with greater risk of reintubation. Both the MIP and MEP were lower in episodes that required reintubation, but the difference did not reach statistical significance. A wide spread was found in the values of blood gases and respiratory function test results in episodes that required reintubation. We could not establish a set of results that could uniformly predict successful extubation, and previously proposed guidelines failed to predict extubation outcome in several patients.

Factors that predict extubation failure may be considered indicators of refractory crisis. Variables associated with extubation failure, such as previous crisis and longer duration of intubation, may be useful for anticipating the need for tracheostomy in patients whose conditions do not improve during their crisis. Timely tracheostomy may facilitate suctioning of respiratory secretions, may prevent pulmonary complications, and may increase patients' comfort.

Atelectasis was the only variable associated with increased likelihood of extubation failure and reintubation. In fact, atelectasis was uniformly present in patients who required reintubation. This finding is concordant with a previous study[7] from a different medical center that also identified atelectasis as the strongest predictor of reintubation among 26 episodes of MC; in that study, atelectasis was also present in all patients who required reintubation (n=7).

The finding that BiPAP use after extubation was associated with increased chances of reintubation appears surprising at first glance. However, BiPAP was used in a few episodes, and it is possible that BiPAP was preferentially tried in patients who were considered at high risk for reintubation or were already showing signs of respiratory fatigue. Such a pattern of use could have produced a bias against BiPAP. Timely BiPAP use after extubation can be effective in averting reintubation in selected patients with MC.[6] To determine the true value of BiPAP after extubation in patients with MC adequately, a randomized controlled study should be performed.

Our study has limitations. The size of our population was not sufficient to allow a multivariate analysis to evaluate for independent associations. This caveat is important when interpreting some of our results, such as the unexpected association between BiPAP use after extubation and increased risk of reintubation. We analyzed the predictive value of single measurements of PFTs and ABG at extubation, following published guidelines that rely on 1-time measurements. However, the trend of these physiologic parameters from intubation until extubation may be more informative and this possibility deserves to be studied.

Extubation failure is common in patients intubated for MC. The resulting prolongation of ICU and hospital stays predisposes patients to in-hospital complications and greatly increases the financial cost of their medical care. The best strategy for preventing this complication would be one that avoids endotracheal intubation altogether, and it has been previously shown that early institution of noninvasive ventilation may achieve this goal.[11,12] Thus, we advocate starting noninvasive ventilation in myasthenic patients as soon as early signs of ventilatory compromise become apparent. Once patients are intubated, implementing programs of aggressive respiratory therapy may reduce the incidence of pulmonary complications (including atelectasis, the strongest predictor of reintubation),[5] which in turn may shorten the ventilation requirement and increase the chances of successful extubation.

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