Noninvasive Ventilation in Myasthenic Crisis

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Background: Myasthenic crisis (MC) is often associated with prolonged intubation and with respiratory complications.

Objectives: To assess predictors of ventilation duration and to compare the effectiveness of endotracheal intubation and mechanical ventilation (ET-MV) with bi-level positive airway pressure (BiPAP) noninvasive ventilation in MC.

Design: Retrospective cohort study.

Setting: Academic research.

Patients: We reviewed consecutive episodes of MC treated at the Mayo Clinic, Rochester, Minnesota.

Main Outcome Measures: Collected information included patients' demographic data, immunotherapy, medical complications, mechanical ventilation duration, and hospital lengths of stay, as well as baseline and preventative measurements of forced vital capacity, maximal inspiratory and expiratory pressures, and arterial blood gases.

Results: We identified 60 episodes of MC in 52 patients. BiPAP was the initial method of ventilatory support in 24 episodes and ET-MV was performed in 36 episodes. There were no differences in patient demographics or in baseline respiratory variables and arterial gases between the groups of episodes initially treated using BiPAP vs ET-MV. In 14 episodes treated using BiPAP, intubation was avoided. The mean duration of BiPAP in these patients was 4.3 days. The only predictor of BiPAP failure (ie, requirement for intubation) was a PCO2 level exceeding 45 mm Hg on BiPAP initiation (P = .04). The mean ventilation duration was 10.4 days. Longer ventilation duration was associated with intubation (P = .02), atelectasis (P < .005), and lower maximal expiratory pressure on arrival (P = .02). The intensive care unit and hospital lengths of stay statistically significantly increased with ventilation duration (P < .001 for both). The only variable associated with decreased ventilation duration was initial BiPAP treatment (P < .007).

Conclusions: BiPAP is effective for the treatment of acute respiratory failure in patients with myasthenia gravis. A BiPAP trial before the development of hypercapnia can prevent intubation and prolonged ventilation, reducing pulmonary complications and lengths of intensive care unit and hospital stay.

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Myasthenic crisis (MC) is defined by the appearance of acute neuromuscular respiratory failure requiring mechanical ventilation. Traditionally, patients with MC are managed using endotracheal intubation and mechanical ventilation (ET-MV), which explains why class V in the Myasthenia Gravis Foundation of America's clinical classification is defined by intubation. Improvements in respiratory care were primarily responsible for the dramatic reduction in mortality among patients with MC that occurred in the 1970s. Despite the introduction of effective immunotherapies (plasma exchange and intravenous immunoglobulin), prolonged care in the intensive care unit (ICU) is still necessary for many patients. The development of pulmonary complications (atelectasis and pneumonia) after ET-MV is probably the most frequent cause for lengthier ICU stays. Therefore, averting ET-MV could have a strong beneficial effect on duration of hospitalization and on cost of care.

Bilevel positive airway pressure (BiPAP) noninvasive ventilation may offer a viable alternative to ET-MV, as suggested by previous findings. Noninvasive ventilation seems desirable in patients with MC because prolonged ET-MV is associated with higher risk of ventilator-associated pneumonia and other systemic complications.

BiPAP has been successfully used to treat acute respiratory failure from cardiopulmonary illnesses and chronic neuromuscular disorders with ventilatory com-
promise. Through a face mask, BiPAP machines deliver adjustable degrees of continuous positive pressure, which is highest during inspiration and lower during expiration. Each cycle is triggered by the patient's breathing effort. Inspiratory positive pressure helps overcome upper airway resistance and reduces the work of breathing. End-expiratory positive pressure prevents airway collapse at the conclusion of each breathing cycle, diminishing the risk of atelectasis. This type of ventilatory support fits well the needs of fatigued patients with MC, who remain capable of initiating breaths but cannot move sufficient air volumes to prevent the progression of microatelectasis and to maintain normal gas exchange and who develop problems from upper airway collapse.

We reviewed our experience treating patients with MC to assess the efficacy of noninvasive ventilation using BiPAP in these patients. We sought to identify predictors of noninvasive ventilation outcome and to evaluate which factors predict ventilation duration in MC.

**METHODS**

The study was approved by our institutional review board. We retrospectively identified all patients with MC admitted to the Mayo Clinic ICU and neurology ICU between January 1987 and December 2006. Myasthenic crisis was defined as acute exacerbation of muscle weakness leading to neuromuscular respiratory failure requiring invasive (ET-MV) or noninvasive (BiPAP) ventilatory support. Postthymectomy patients (n=10), patients with Lambert-Eaton syndrome (n=1), and patients with congenital myasthenia (n=6) were excluded from the study. One patient with MC who was initially seen in respiratory distress due to a pneumothorax was excluded. Patients with MC who were intubated for respiratory failure because of cardiac failure and underlying respiratory disease were also excluded. All patients had severe generalized and bulbar weakness.

A clinical diagnosis of MC was confirmed in all patients by 1 or more of the following investigations: repetitive nerve stimulation, acetylcholine receptor antibody positivity, or single-fiber electromyographic testing. The general criteria to consider ventilation were forced vital capacity less than 15 to 20 mL/kg of body weight, maximal inspiratory pressure (MIP) less than −40 cm of water, maximal expiratory pressure (MEP) less than 40 cm of water, or evidence of respiratory muscle fatigue, hypercapnia, or hypoxia. However, these criteria were used as guidelines, and the timing of initiation of ventilation and the decision to intubate depended on the clinical assessment and practice preference of the emergency department staff or intensivist in the ICU.

We collected patients’ demographic and clinical information, including age, sex, weight, previous crisis, history of thymoma, treatment on admission, time from diagnosis to present crisis, acetylcholine receptor antibody positivity, trigger factors (eg, infection, surgery, or change of medications), and other medical history (lung disease, smoking history, diabetes mellitus, cancer, or cardiac failure). The presence of lung disease was determined by the documented diagnosis of asthma, restrictive lung disease, obstructive sleep apnea, or chronic obstructive pulmonary disease.

Arterial blood gases and bedside pulmonary function test results (forced vital capacity [FVC] in milliliters per kilogram of body weight, MIP, and MEP) were recorded when available on admission, before BiPAP or intubation, and on extubation or discontinuation of BiPAP. Bedside pulmonary function tests were performed using a scuba-like device that reduced air leak-

age. Arterial-alveolar gradients were calculated using the alveolar air equation. Duration of BiPAP or intubation (total ventilation duration) was recorded. If a patient required reintubation or BiPAP during the same ICU admission, this period was included in the total ventilation duration.

The medical treatment initiated (plasmapheresis, intravenous immunoglobulin, or intravenous corticosteroids) in the ICU was recorded. Weaning of ventilated patients was not attempted until adequate medical treatment had been initiated. The use of a T-piece or BiPAP support after extubation was recorded. In patients who failed extubation, we collected the time of reintubation, cause of reintubation (fatigue, atelectasis, or lobar collapse), and complications from extubation failure. When applicable, the timing of tracheostomy was noted.

All medical complications during the ICU stay were recorded, with the major categories being atelectasis, pneumonia, bronchitis, cardiac arrest, and sepsis. Chest radiographs were reviewed for the presence of atelectasis and consolidation. Atelectasis was defined by unequivocal radiological evidence of segmental or lobar collapse. The diagnosis of pneumonia required the presence of fever, new infiltrate on chest radiographs, and positive culture of respiratory secretions. The ICU length of stay and the total hospital length of stay were tabulated. Functional status and disposition at discharge (home, rehabilitation facility, or nursing home) were also collected.

We analyzed predictors of outcome in patients treated using noninvasive ventilation. Failure of noninvasive ventilation was determined by a requirement for intubation after BiPAP trial. Predictors of longer duration of mechanical ventilation were evaluated in our entire population. Ventilation duration was computed by adding the duration of BiPAP use and the duration of invasive ventilation (synchronized intermittent mandatory ventilation or pressure support of ≥7 mm Hg).

Descriptive summaries were given as means and ranges for continuous variables and as frequencies and percentages for categorical variables. Baseline demographic and physiological variables among the 3 groups (BiPAP success, BiPAP failure, and ET-MV) were compared using Kruskal-Wallis test or χ² test based on whether the variable was continuous or categorical. Similarly, comparisons of clinical end points between groups receiving initial BiPAP vs initial ET-MV were made using the Wilcoxon rank sum test or χ² test (or Fisher exact test) as appropriate. Nonparametric tests were used because of small sample sizes and non-Gaussian distribution of the data. Univariate logistic regression analysis was used to assess the association between the several potential predictors and ventilation duration as binary outcome variables. Associations were reported in terms of odds ratios and 95% confidence intervals. All tests were 2-sided, and P < .05 was considered statistically significant.

We identified 60 episodes of MC in 52 patients treated using BiPAP or ET-MV. BiPAP was tried initially in 24 episodes (40%) and ET-MV was performed without preceding BiPAP trial in 36 episodes (60%). Ten episodes initially treated using BiPAP subsequently required ET-MV during the same admission (ie, BiPAP failure). Therefore, 46 of 60 patients (77%) in our population were intubated for the treatment of their MC.

The mean patient age was 62.0 years (age range, 17-90 years), and 52% (32) were women. The median disease duration from diagnosis to presentation with MC was 4 years (range, 1 month to 43 years). Thymoma was documented in 19 patients (42%), previous crisis in 17 patients (43%), and lung disease in 12 patients (22%). Ace-
Bulbar weakness was uniformly present. Fourteen patients (58%) were successfully treated using BiPAP. The median age was 61 years (age range, 17-90 years). The median disease duration was 4 years (range, 0.08-43 years), 11 patients (46%) had a history of thymoma. All patients had acetylcholine receptor antibodies. Anti-MuSK (muscle-specific receptor tyrosine kinase) antibody was not present in any of the patients. The mean (SD) duration of BiPAP use in these successful cases was 4.3 (2.9) days. The FVC, MIP, MEP, and PO2 level on admission or on BiPAP initiation failed to predict outcome of noninvasive ventilation, although pulmonary function tests on BiPAP initiation were not performed in 9 patients (38%). Trigger factors, type of immunotherapy administered, and history of crisis or preexisting lung disease also failed to predict outcome of BiPAP treatment. The only predictor of BiPAP failure was a PCO2 level exceeding 45 mm Hg on BiPAP initiation (P = .04).

The mean (SD) ventilation duration in the entire population was 10.4 (11.1) days. Ventilation duration was 5.6 days (range, 1.5-21.0 days) in patients initially treated using BiPAP vs 13.6 days (range, 3-60 days) in patients initially treated using ET-MV. When assessing ventilation duration as a continuous variable, longer ventilation duration was associated with ET-MV use (P = .02), and the development of atelectasis (P < .005). The only variable associated with decreased ventilation duration was BiPAP treatment (P < .007). Ventilation duration longer than 7 days (which was the median ventilation duration for the entire population) was associated with ET-MV use, atelectasis, lower MEP on arrival (P = .02), and the development of atelectasis (P < .005). The only variable associated with lower likelihood of ventilation duration longer than 7 days was BiPAP use (Table 2).

The median ICU length of stay for the entire study population was 10.5 days (range, 1-60 days), and the me-
median hospital length of stay was 17 days (range, 1-123 days). The intensive care unit and hospital lengths of stay statistically significantly increased with ventilation duration ($P < .001$ for both). Initial BiPAP use statistically significantly shortened these stays by one-third (median, 7 days). Rates of pulmonary complications, atelectasis, and pneumonia did not differ between the patients initially treated using BiPAP vs ET-MV. However, the difference was statistically significant when patients successfully treated using BiPAP vs patients treated using ET-MV (ie, BiPAP failure plus initial ET-MV) were compared ($321\%$ vs $2554\%$, $P = .04$). Table 3 summarizes the differences in pulmonary complications and lengths of stay between patients initially treated using BiPAP vs ET-MV. Two patients died of complications from their MC, resulting in a mortality rate of $3.3\%$. Both deaths occurred in patients initially treated using ET-MV.

In this analysis of 60 episodes of MC, initial treatment using BiPAP was associated with shorter ventilation duration and ICU stay compared with patients managed using the conventional strategy of ET-MV. This benefit may have been because of the decreased rates of pulmonary complications among patients successfully treated using BiPAP. When instituted early, BiPAP avoided the use of ET-MV, but the presence of hypercapnia at the time of BiPAP initiation predicted failure of noninvasive ventilation and subsequent ET-MV.

Fatigue of the diaphragm and accessory breathing muscles resulting in insufficient air exchange constitutes the most common indication for mechanical ventilation in MC. In addition, upper airway collapse from weakness of oropharyngeal and laryngeal muscles and the inability to clear secretions may precipitate respiratory failure or may contribute to its development.11-13 BiPAP may effectively support the weak respiratory muscles, enhance alveolar recruitment, prevent atelectasis from alveolar collapse, and help overcome the increased upper airway resistance. The concern that accumulation or aspiration of respiratory secretions could limit the usefulness of BiPAP in patients with MC is not substantiated by the results of this study, as patients treated in a timely manner using BiPAP had low rates of pneumonia.

To assess the validity of our findings, we compared our groups of patients initially treated using BiPAP vs ET-MV. There were no differences in serologic status, comorbid conditions, demographic variables, duration of myasthenia, history of thymoma or crisis, or distribution of precipitants for the crisis. Furthermore, arterial blood gases and respiratory function test results were comparable on arrival to the emergency department, indicating that the patients had similar degrees of respiratory compromise. Patients were also similarly treated using immunotherapy during their hospitalization. Hence, baseline differences did not seem to have accounted for the better results observed in patients initially treated using BiPAP.

The baseline characteristics of our patient population (ie, age, disease duration, and triggering factors) were comparable with those of previously reported large case series.8,10 As in other series, our patients were treated using immunotherapy (plasma exchange or intravenous immunoglobulin [and sometimes intravenous corticosteroids]). Our overall rates of pulmonary complications and ICU lengths of stay were in the lower ranges of those previously reported,8,10 mostly because of the lower incidence of pulmonary complications and the shorter ICU lengths of stay in patients successfully treated using BiPAP. Therefore, the population of patients with MC presented herein is comparable to other large published series, except for the use of noninvasive ventilation.

Bedside variables of respiratory function, pulmonary function test results (FVC, MIP, and MEP), and arterial blood gases had limited predictive value in our study, with few exceptions. Results of tests of pulmonary function measured on arrival to the emergency department and before BiPAP initiation failed to predict the outcome of noninvasive ventilation. The small size of the population under study for this part of the analysis and the lack of measurement of pulmonary function immediately before BiPAP initiation in approximately one-third of patients treated using noninvasive ventilation may have limited our ability to assess the predictive value of these tests. Nonetheless, hypercapnia (PCO$_2$ level, $>45$ mm Hg) on arterial blood gas measurement was associated with BiPAP failure. Conversely, arterial blood gas measures on arrival and at the

### Table 2. Predictors of Ventilation Duration Longer Than 7 Days Among 60 Episodes of Myasthenic Crisis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of crisis</td>
<td>3.08 (1.02-9.28)</td>
<td>.05</td>
</tr>
<tr>
<td>History of thymoma</td>
<td>3.14 (1.07-9.19)</td>
<td>.04</td>
</tr>
<tr>
<td>Initial maximal expiratory pressure$^a$</td>
<td>0.96 (0.93-0.99)</td>
<td>.05</td>
</tr>
<tr>
<td>Intravenous corticosteroid use</td>
<td>3.97 (1.06-14.85)</td>
<td>.04</td>
</tr>
<tr>
<td>Initial endotracheal intubation and mechanical ventilation$^b$</td>
<td>6.54 (1.32-32.56)</td>
<td>.02</td>
</tr>
<tr>
<td>Atelectasis$^b$</td>
<td>8.50 (1.46-49.54)</td>
<td>.02</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.75 (0.95-14.82)</td>
<td>.06</td>
</tr>
<tr>
<td>Initial bilevel positive airway pressure$^b$</td>
<td>0.24 (0.08-0.70)</td>
<td>.01</td>
</tr>
</tbody>
</table>

$^a$ Also statistically significantly associated with ventilation duration when analyzed as a continuous variable.

### Table 3. Clinical End Points in Episodes of Myasthenic Crisis Initially Treated Using BiPAP vs ET-MV$^a$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial BiPAP$^b$ (n=24)</th>
<th>Initial ET-MV (n=36)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation duration, d</td>
<td>4 (1.5-21)</td>
<td>9 (3-60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>27</td>
<td>37</td>
<td>.70</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>53</td>
<td>44</td>
<td>.74</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>7 (2-42)</td>
<td>13 (4-60)</td>
<td>.002</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>13 (2-60)</td>
<td>20 (4-123)</td>
<td>.03</td>
</tr>
<tr>
<td>Hospital</td>
<td>0</td>
<td>6</td>
<td>.36</td>
</tr>
</tbody>
</table>

$^a$ Ten patients failed BiPAP trial and required ET-MV.

Abbreviations: BiPAP, bilevel positive airway pressure; ET-MV, endotracheal intubation and mechanical ventilation.
time of BiPAP initiation or ET-MV did not predict ventilation duration, but patients with initial lower MEP were at risk for requiring prolonged ventilation.

Lower MEP on arrival, the development of atelectasis, and initial ET-MV were the variables most consistently associated with prolonged ventilation. Initial BiPAP was the only factor associated with lower risk of long ventilatory requirement. This association may have resulted from the lower rate of pulmonary complications in patients successfully treated using BiPAP only. However, patients in whom BiPAP failed had high rates of pulmonary complications (present in 8 of 10 patients) that often resulted in prolonged ventilation (5 of 10 patients needed ventilation for >10 days). Hence, initial treatment using BiPAP may decrease the risk of prolonged ventilatory requirement, but early institution of noninvasive ventilation, before the development of hypercapnia, is crucial to achieve this goal.

The main limitation of our study is that the criteria for initiating ventilation and choosing the initial mode of ventilation (noninvasive or invasive) were not uniform. These decisions were made by the treating physicians based on some general guidelines (see the “Methods” section) but were often mostly based on personal preferences. This practice variation explains why patients with similar disease severity were sometimes initially treated using BiPAP and at other times using ET-MV. The lack of statistically significant differences in the initial measures of respiratory muscle strength (FVC, MIP, and MEP) and gas exchange (arterial blood gases) between the 2 treatment groups supports the validity of the comparison, although the small size of the subpopulations compromises the power of the analysis. Hence, our findings should be best interpreted as raising a hypothesis that needs to be tested in a randomized controlled study.

The results of this study indicate that noninvasive ventilation using BiPAP should be considered in selected patients with MC who have respiratory compromise (those without hypercapnia and with the ability to synchronize with the machine) as the initial method of ventilatory support. We believe that a randomized trial comparing BiPAP vs ET-MV in patients with MC should be undertaken.

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REFERENCES