Review article

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# The effectiveness of noninvasive ventilation in myasthenia gravis subjects with respiratory failure in reducing the need of endotracheal intubation and increase extubation outcomes

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**Abstract**

***Background*: Myasthenia gravis is characterized by muscle weakness and fatigability. The affected muscle are ocular muscle, oropharyngeal muscle, facial muscle, and respiratory muscle. This leads to respiratory failure in myasthenia gravis patients with myasthenic crisis. Noninvasive ventilation has been used to treat patients with hypercapnia respiratory failure and associated with reduction of the need of endotracheal intubation, reduction of complication rate, reduction of hospital stays, and reduction of mortality. In myasthenia gravis patients with respiratory failure, there is no evidence that noninvasive ventilation would reduce those factors. Thus, we studied the effectiveness of noninvasive ventilation in myasthenia gravis patients with respiratory failure in reducing the need of endotracheal intubation and increase extubation outcomes.**

***Methods*: Literature review on PubMed, Elton B. Stephens Co. (EBSCO), Cochrane, and ScienceDirect yield two relevant articles.**

***Results*: Two studies showed that noninvasive ventilation in subject with myasthenia gravis with respiratory failure had better effect.**

***Conclusion*: It is effective to use noninvasive ventilation in subject with myasthenia gravis during their respiratory failure in myasthenic crisis.**

**Key words**: Myasthenia gravis, respiratory failure, noninvasive ventilation, airway extubation, intubation.

## Introduction

Myasthenia gravis is an acquired autoimmune disorder characterized by muscle weakness and fatigability. Subjects usually come to the doctor complaining about their specific muscle weakness. Ocular symptoms are the first manifestation of myasthenia gravis and its typical ocular symptoms are ptosis, diplopia, with or without blurred vision. This ocular symptom presents as first manifestation in 40% of myasthenia gravis subjects and involve in 85% of myasthenia gravis subjects. The other affected muscle weaknesses are oropharyngeal muscle weakness, facial weakness, and respiratory muscle weakness. This autoimmune disorder mistakenly attacks the connection between the nerve and the muscle, called neuromuscular junction. It inhibits acetylcholine to bind its receptor to send a signal to the muscle to do their jobs. This leads to muscle weakness. (1-4)

Myasthenic crisis is a life-threatening condition marked by worsening symptoms of muscle weakness, especially respiratory muscle weakness, that requires intubation or noninvasive ventilation as respiratory assistant. Respiratory muscle weakness leads to respiratory failure in most of myasthenia gravis subjects. Respiratory failure happens due to inadequate gas exchange in lungs. As a result, subjects cannot maintain pH, pO2, and pCO2 in normal range and hypoxemia occurs with or without hypercapnia. Invasive or noninvasive ventilation has their own indication to be applied. Invasive ventilation or mechanical ventilation is the most widely used ventilation in intensive care unit to manage acute respiratory failure or acute respiratory distress. Noninvasive ventilation, such as con-

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tinuous positive airway pressure and bi-level positive airway pressure, has been used to treat subjects with hypercapnia respiratory failure or subjects with acute exacerbation of chronic obstructive pulmonary disease. Noninvasive ventilation is associated with reduction of the need of endotracheal intubation, reduction of complication rate, reduction of hospital stays, reduction of mortality, and increase extubation outcomes. Noninvasive ventilation was considered successful in extubation outcomes if they do not require intubation 72 hours right after extubation. (1-4)

In myasthenia gravis patients with respiratory failure, there is no evidence that noninvasive ventilation would reduce the need of endotracheal intubation, complication rate, hospital stay, or even mortality. We studied the effectiveness of noninvasive ventilation in myasthenia gravis patients with respiratory failure in reducing the need of endotracheal intubation and increase extubation outcomes. (1-4)

## Case illustration

Mr. FD, 36-year-old, admitted to the hospital on 15th December 2017 with chief complaint of dyspnea that worsen. Patient was first diagnosed with myasthenia gravis 14 years ago with ocular myasthenia gravis. He had been suffering unilateral ptosis, muscle weakness, respiratory failure, and difficulty to swallow. On his routine medical checkup, the thorax scan result showed that there was thymoma in his neck. He underwent the thymectomy procedure, but he suffered from respiratory failure right after the procedure. He underwent continuous positive airway pressure (CPAP) therapy as his respiratory assistant. As a doctor, I was wondering the effectiveness of CPAP, one of noninvasive ventilation, as his respiratory assistant in reducing the need of endotracheal intubation and increase extubation outcomes.

## Clinical question

In myasthenia gravis patients with respiratory failure, is noninvasive ventilation effective in reducing the need of endotracheal intubation and increase extubation outcomes?

## Methods

*Search strategy*

Literature review was conducted on March 2018 from four online databases: PubMed, Cochrane, Elton B. Stephens Co. (EBSCO), and ScienceDirect, using the keywords with synonym and related items (**Table 1**). The search strategy and results are described in **Figure 1**.

*Selection*

The results from databases were first selected based on article duplication. Before that, articles from ScienceDirect were screened to find a suitable title due to abundant results. After excluding duplicated papers, the selection was conducted on title and abstract using inclusion and exclusion criteria. The studies were eligible for inclusion if they were myasthenia gravis patients with respiratory failure treated with noninvasive ventilation. The exclusion criteria for studies were myasthenia gravis subject with respiratory failure treated with invasive ventilation, myasthenia gravis subject without respiratory failure or insufficiency, and if the full text of the reports were not available.

*Critical appraisal*

The selection articles were critically appraised to assess its quality. The aspects that were assessed included validity, importance, and applicability for therapy study. The parameters that were used to assess were: whether the sample that was recruited sufficiently represented the target population or not, did the groups have similar baseline and were they treated equally, was the assignment of sample to treatment randomized and was the randomization list concealed, was there blinding objective manner, was it applicable to patients?

*Critical appraisal results*

The validity, importance, and applicability of the chosen articles were identified in **Table 2**. Furthermore, the study results contained in the contingency table of **Table 3**.

## Results

An initial search conducted on March 2018 resulted in 166 articles from 4 databases. After the selection based on inclusion and exclusion criteria, 2 articles were considered to be the most relevant studies hence were selected. Two articles with full-text were not available online. Within those articles, one was a retrospective cohort by Seneviratne, 2008 from EBSCO, and the other one was also a retrospective study from EBSCO by Yu Wu, 2013.

The first report, which was reported by Yu Wu, et al was a 7-year cohort study in National Taiwan University Hospital. The patients with myasthenia gravis were selected from electronic database medical record in that hospital. The diagnosis of myasthenia gravis was based on patient's clinical symptoms and their serologic test results. Patient included in this study were either intubated for mechanical ventilation or assisted by noninvasive ventilation as their respiratory assistant. Intubation decision based on patient's clinical manifestation and their arterial blood gas (ABG) results. This study excluded patients with cardiac arrest, tracheostomy before using ventilator, and duration of mechanical ventilation <2 days. The patient's medical records were reviewed and their demographics, pulmonary function, ABG results, treatment modalities, and extubation outcome were recorded. In this study, noninvasive ventilation success was defined as being free from intubation and did not require intubation 72 hours right after extubation. The decision of extubation was decided by neurologist and received immunosuppressive therapy, plasma exchange, and has passed spontaneous breathing trial (SBT). This trial included a trial with T-piece, a trial with low pressure support (<6 cmH2O) and low positive end-expiratory pressure (<5 cmH2O), and a trial of automatic tube compensation mode. Spontaneous breathing trial was said as success if the patient has calm general appearance, stable hemodynamic profile and cardiac rhythm, oxygen saturation >90% on pulse oximetry with fraction of inspired oxygen below 40%, and the need of sputum suction during SBT. If the patient could not maintain his/her spontaneous breathing 72 hours right after extubation, then it was called extubation failure. Baseline data were similar between noninvasive ventilation and invasive ventilation presented in the original publication. There were also no differences in physiological data and demographic data between extubation success and extubation failure. (5,6)

In this study, there were 199 patients with myasthenia gravis and 41 episodes (12.4%) of them were due to respiratory failure in myasthenic crisis. Noninvasive ventilation was initially used in 14 patients, and the other 27 patients were initially intubated and underwent mechanical ventilation. Six of the 14 (42.9%) patients required intubation because of noninvasive ventilation failure. The other 8 (57.1%) patients were successfully prevented from intubation, or we called it noninvasive ventilation success. The outcomes were significantly better in the eight patients with noninvasive ventilation success compared to 33 patients who were intubated and underwent mechanical ventilation. Noninvasive ventilation success patients had a shortened length of stay in the ICU, 2 days compared to 8 days in noninvasive ventilation failure patients. Noninvasive ventilation success patients had also a reduced duration of hospitalization, 20 days compared to 44 days in noninvasive ventilation failure patients. (5,6)

Among the 33 episodes of intubation and mechanical ventilation, extubation success was achieved in 20 patients (60.6%), 6 patients with noninvasive ventilation failure, and the other twelve patients with invasive mechanical initiation. The remaining 13 patients with extubation failure were leading to reintubation because of poor cough power with sputum impaction, respiratory distress, CO2 retention, and desaturation. None of the patients in the extubation failure group had previous diagnosis of asthma, chronic obstructive pulmonary disease, or even congestive heart failure. There were no differences in the demographic and physiological data on ICU admission between extubation success group and extubation failure group. Patients with extubation success had significant higher values of maximal inspiratory pressure (Pimax) and maximal expiratory pressure (Pemax) as compared to those in the failure group. A Pemax ≥40 cmH2O was a good predictor of extubation success. A Pimax >30 cmH2O was also a predictor of extubation success, but it has low specificity. (5,6)

Their study results also showed the role of noninvasive ventilation application after extubation. Intermittent noninvasive ventilation was applied to 10 of 33 patients that underwent invasive mechanical ventilation after extubation. Seven of them received noninvasive ventilation less than 6 hours per day and were successfully prevented from reintubation, whereas the other three patients were not. However, there were no significant differences in demographics and physiological parameters between those two groups. (5,6)

The second study conducted by Seneviratne, et al was a 19 years cohort study in America. Patients with Lambert-Eaton syndrome and congenital myasthenia were excluded from this study. Patient with myasthenic crisis, who was initially seen in respiratory distress syndrome due to pneumothorax, was also excluded. There were 60 episodes of myasthenic crisis in 52 patients. bilevel positive airway pressure (BiPAP), as a noninvasive ventilation, was applied in this study and an initial method of ventilatory support in 24 episodes. Mechanical ventilation was performed in the other 36 episodes. There were no differences in patient's demographics or their baseline respiratory variables and arterial blood gasses results between the groups of episodes initially treated using noninvasive ventilation and invasive ventilation. Fourteen episodes of myasthenic crisis that were treated using noninvasive ventilation successfully avoid intubation. The other 10 patients underwent BiPAP failure required intubation and mechanical ventilation. Therefore, there were 46 patients who were intubated and treated with mechanical ventilation.

There was no difference of baseline demographic and physiological data of those patients treated initially using BiPAP and those patients that were treated using mechanical ventilation. Ventilation duration was 4 days in patients initially treated using BiPAP compared to 10 days in patients initially treated using mechanical ventilation. The only factor of noninvasive failure was a pCO2 level exceeding 45 mmHg on noninvasive ventilation initiation. Longer ventilation duration was associated with intubation and invasive ventilation, atelectasis, and lower maximal expiratory pressure on arrival. The intensive care unit and hospital lengths of stay increased with invasive ventilation. The only variable associated with decreased ventilation duration was initial BiPAP treatment. (5,6)

**Discussion**

From two studies above, we can see that evidence almost consistently showing that noninvasive ventilation had a better effect to reduce the need of intubation and increasing extubation outcome. Initial treatment using noninvasive ventilation was associated with shorter ventilation duration and hospital length of stay compared with patients that were managed using mechanical ventilation. This was because of the reduction rates of pulmonary complications in patients that were treated using noninvasive ventilation. (5,6)

Upper airway collapse in myasthenia gravis from oropharyngeal weakness and laryngeal muscle weakness leading to respiratory failure. Noninvasive ventilation supports the weak respiratory muscles, enhance the alveolar recruitment, prevent atelectasis from alveolar collapse, and helps overcome the increased of upper airway resistance. That is why noninvasive ventilation associated with the reduction of pulmonary complications in patients that are treated using noninvasive ventilation. The application of noninvasive ventilation can augment airflow and prevents airway collapse by offering positive airway pressure both in the inhalation and exhalation phases of respiration. Noninvasive ventilation that commonly used are CPAP and BiPAP. They are usually used and applicable in Indonesia. (1-4,7)

Predictors of noninvasive ventilation success, based on the result of the second study, included younger age, lower severity of disease, better neurological score, and moderate respiratory acidosis. The only factor of noninvasive ventilation failure was a pCO2 level exceeding 45 mmHg on noninvasive ventilation initiation. Therefore, evaluation before and during the treatment is a must to maintain patient's condition. (5,6)

Ventilation failure is a common cause of mortality among patients with myasthenia gravis, as a consequence invasive ventilation can be avoided if the patient can be treated using noninvasive ventilation. It's not only about ventilation failure, but those two studies also examined the impact of extubation failure. Extubation means that patients can breath freely without any respiratory assistance. In the first study, among 33 episodes of intubation and mechanical ventilation, extubation success was achieved in 20 patients. The remaining 13 patients with extubation failure needed reintubation because of poor cough power with sputum impaction, respiratory distress, CO2 retention, and desaturation. None of the patients in the extubation failure group had a previous diagnosis of asthma, chronic obstructive pulmonary disease, or even congestive heart failure. So, there was no bias that can influence the extubation outcomes in this study. Prolonged intubation, or we can call it extubation failure, however, may lead to several complications such as atelectasis, anemia, urinary tract infection, and congestive heart failure. Thus, the success of extubation reduce the morbidity and mortality of these patients. (5,6)

The main limitation of the first and the second study were that the criteria for initiating ventilation were unclear. These decisions were made by the treating physicians, which were based on personal preferences. The other limitation in both studies were their study design, a single-centered, retrospective study, and the sample size was too small to represent a population. But in this case, myasthenia gravis is such a rare disease, so a cohort design is the best study design for this kind of disease. The other limitation for both studies were heterogeneity of the data among the study population because of its study duration 7 years and 19 years. We believe that a randomized trial comparing noninvasive ventilation and invasive ventilation in patients with myasthenic crisis should be applied. (5,6)

**Conclusion**

In summary, noninvasive ventilation is effective for the treatment in myasthenia gravis patients with respiratory failure. Noninvasive ventilation reduces the need of intubation and mechanical ventilation, increase extubation outcome, reduce duration of ventilation, reduce pulmonary complication, and reduce the lengths of hospital stay.

**Table 1**. Search strategy used in PubMed, Cochrane, EBSCO and ScienceDirect

| Database | Search terms | Results |
|---|---|---|
| PubMed | (("Myasthenia Gravis"[Mesh] OR "Myasthenia Gravis, Autoimmune, Experimental"[Mesh]) AND ("Respiratory Insufficiency"[Mesh] OR "Respiratory Distress Syndrome, Adult"[Mesh])) AND ("Noninvasive Ventilation"[Mesh] OR "Continuous Positive Airway Pressure"[Mesh]) AND ("Airway Extubation"[Mesh] OR "Intubation"[Mesh])) | 2 |
| Cochrane | ("Myasthenia Gravis" OR "Myasthenia Gravis, Autoimmune, Experimental") AND ("Respiratory Insufficiency") AND ("Positive-Pressure Respiration" OR "Noninvasive Ventilation" OR "Continuous Positive Airway Pressure") AND ("Airway extubation" OR "Intubation") | 0 |
| EBSCO | ("Myasthenia Gravis" AND "Respiratory Failure") AND ("Positive-Pressure Respiration" OR "Noninvasive Ventilation" OR "Continuous Positive Airway Pressure") AND ("Airway extubation" OR "Intubation") | 5 |
| ScienceDirect | (("Myasthenia Gravis" OR "Autoimmune Myasthenia Gravis") AND ("Respiratory Insufficiency" OR "Respiratory Failure")) AND ("Positive Pressure Respiration" OR "Noninvasive Ventilation" OR "Continuous Positive Airway Pressure" OR "CPAP") AND ("Airway Extubation" OR "intubation") | 159 |

Legend: EBSCO=Elton B. Stephens Co.

**Table 2**. Results of all studies

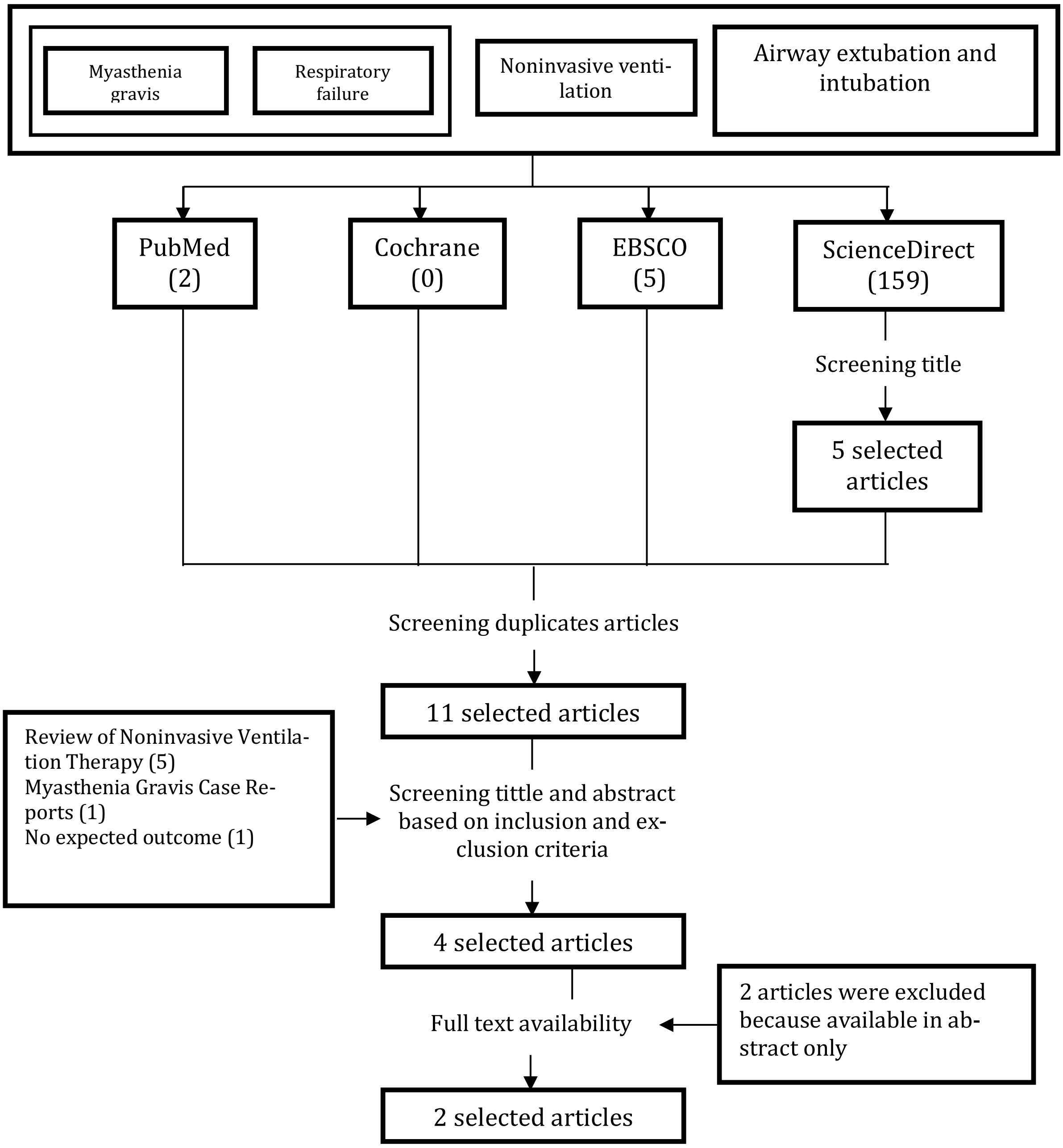
| Parameters | Seneviratne, 2008 | Yu Wu, 2009 |
|---|---|---|
| Validity | | |
| - Randomized | Consecutive sampling | Consecutive sampling |
| - Similar at start | + | + |
| - Equal treatment | + | + |
| - Follow-up | + | + |
| - Intention to treat | + | + |
| - Blinding | - | - |
| Importance | | |
| - CER | 55% | 57% |
| - EER | 58% | 58% |
| - RRR | 0.05 | 0.01 |
| - ARR | -3% | -1% |
| - NNT | 33.3 | 100 |
| - CI on ARR | ±16.80% | ±20.78% |
| Applicability | | |
| - Result to own patients | + | + |
| - NNT to own patients | 0.05 | 0.03 |
| - Statistically significant | + | + |
| - Clinically important | - | - |

Legend: CER=control event rate; EER=experimental event rate; RRR=relative risk reduction; ARR=absolute risk reduction; NNT=number needed to treat; CI=confidence interval.

**Table 3**. Results of all studies

| Parameter | Seneviratne, 2008 | Yu Wu, 2009 |
|---|---|---|
| Design | Retrospective cohort | Retrospective cohort |
| Study duration | 19 years | 7 years |
| Subjects | 52 patients with 60 episodes of respiratory failure Noninvasive ventilation was assigned in 24 episodes of respiratory failure, 36 episodes was supported by mechanical ventilation | 199 patients with 41 episodes of respiratory failure Noninvasive ventilation was assigned in 14 episodes of respiratory failure, 27 episodes was supported by mechanical ventilation |
| Avoided intubation in noninvasive ventilation | 24 episodes | 8 episodes |
| Mean duration of noninvasive ventilation | 4 days | 2 days |
| Mean duration of invasive ventilation | 10 days | 20 days |
| Noninvasive ventilation failure factors as in intubation requirement | pCO2 level exceeding 45 mmHg on noninvasive ventilation initiation | Same baseline between noninvasive ventilation failure and success |
| Extubation success after noninvasive ventilation | 14 episodes | 6 episodes |
| Duration of hospitalization in patients with noninvasive ventilation | 13 days | 20 days |
| Duration of hospitalization in patients without noninvasive ventilation | 20 days | 44 days |

**Figure 1**. Searching strategy



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