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Early Tracheostomy Is Associated With Shorter Ventilation Time and Duration of ICU Stay in Patients With Myasthenic Crisis—A Multicenter Analysis

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Abstract

Background: Myasthenic crisis (MC) requiring mechanical ventilation (MV) is a rare and serious complication of myasthenia gravis. Here we analyzed the frequency of performed tracheostomies, risk factors correlating with a tracheostomy, as well as the impact of an early tracheostomy on ventilation time and ICU length of stay (LOS) in MC. **Methods:** Retrospective chart review on patients treated for MC in 12 German neurological departments between 2006 and 2015 to assess demographic/diagnostic data, rates and timing of tracheostomy and outcome. **Results:** In 107 out of 215 MC (49.8%), a tracheostomy was performed. Patients without tracheostomy were more likely to have an early-onset myasthenia gravis (27 [25.2%] vs 12 [11.5%], $p = 0.01$). Patients receiving a tracheostomy, however, were more frequently suffering from multiple comorbidities (20 [18.7%] vs 9 [8.3%],

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$p = 0.03$) and also the ventilation time (34.4 days $\pm$ 27.7 versus 7.9 $\pm$ 7.8, $p < 0.0001$) and ICU-LOS (34.8 days $\pm$ 25.5 versus 12.1 $\pm$ 8.0, $p < 0.0001$) was significantly longer than in non-tracheostomized patients. Demographics and characteristics of the course of the disease up to the crisis were not significantly different between patients with an early (within 10 days) compared to a late tracheostomy. However, an early tracheostomy correlated with a shorter duration of MV at ICU (26.2 days $\pm$ 18.1 versus 42.0 $\pm$ 33.1, $p = 0.006$), and ICU-LOS (26.2 days $\pm$ 14.6 versus 42.3 $\pm$ 33.0, $p = 0.003$). **Conclusion:** Half of the ventilated patients with MC required a tracheostomy. Poorer health condition before the crisis and late-onset MG were associated with a tracheostomy. An early tracheostomy ($\leq$ day 10), however, was associated with a shorter duration of MV and ICU-LOS by 2 weeks.

Keywords
myasthenic crisis, mechanical ventilation, tracheostomy

Introduction

Myasthenia gravis (MG) is a B-cell mediated autoimmune disease and the most frequent disorder of the neuromuscular junction. In most patients it is associated with pathogenic autoantibodies against components of the postsynaptic membrane such as the acetylcholine receptor (AChR) or the muscle-specific kinase (MUSK). Characteristic symptoms are muscle weakness, dysphagia and fatigue that typically increase throughout continuous muscular activity.[1-3]

Within 2 years of the initial diagnosis 15 to 20% of MG patients develop a potentially life-threatening myasthenic crisis (MC).[4-7] MC has been defined as respiratory failure requiring mechanical ventilation due to respiratory muscle weakness or bulbar dysfunction.[1,6,8] Triggering factors include infection, inadequate drug usage or incorrect treatment.[2,9] The most common of the preceding factors though, is respiratory infection.[6,10]

For the treatment of MC plasma exchange (PE) and intravenous immunoglobulins (IVIG) seem to perform with similar efficacy.[2,7,11-13] In addition to immunotherapy, intubation and mechanical ventilation (MV) as well as the antibiotic treatment of infections are important in the therapy of MC. Extubation failure and reintubation are quite common in patients with neuromuscular diseases[14-18] and has been shown to lead to a prolonged duration of MV and ICU length of stay (ICU-LOS), as well as to a higher incidence of ventilator-associated pneumonia (VAP).[15,16,18] Tracheostomy (TT) is thought to be more comfortable for the patient allowing for a more effective respiratory toilet and reducing volume of anatomical dead space, and therefore facilitating respiration which is especially important for patients with MC.

The benefits of early TT are still controversial in many diseases: some studies found a reduced long-term mortality, shortened weaning and ICU-LOS[19,20,21-25] others found no difference in terms of MV, hospital-LOS, rates of mortality or incidence of VAP.[26-29] The question whether early TT might be beneficial in MC has not yet been addressed.

In this retrospective multicenter study we investigated the rate of TT and the factors associated with the timing of TT in MC patients. Moreover, we investigated whether early TT is associated with shorter duration of MV and ICU-LOS.

Methods

Study Design and Patient Selection

12 German Departments of Neurology with specialized Neuro-Intensive Care Units (NICU) or interdisciplinary ICU took part in the present study. We retrospectively analyzed all patients between 2006 and 2015 admitted during MC requiring invasive mechanical ventilation. Data of patients with the discharge diagnosis of MG according to the International Classification of Diseases (ICD 10: G70.0-70.3) and admission to ICU were reviewed. MC was defined as an exacerbation of myasthenic symptoms with bulbar and/or general weakness requiring mechanical ventilation. Diagnosis of MG had to be established clinically according to national guidelines[30] and confirmed by specific tests (antibody testing or pathological decrement on repetitive nerve stimulation or improvement after cholinergic medication). Exclusion criteria were: pure cholinergic crisis without MG, Lambert Eaton myasthenic syndrome, myasthenic syndromes other than MG (such as congenital MG) and mechanical ventilation within 4 weeks of thymectomy, thus eliminating patients with post-thymectomy crisis. TT decision and timing of TT were made by the physicians in charge. If a patient died in hospital or the exact times of intubation or TT were missing, the patients' data was excluded from statistic evaluation for correlation analysis and comparison of patients with early or late TT.

To compare early versus late TT, we dichotomized the group of tracheostomized patients in 2 equally large groups: according to the median days between intubation and TT, day 10 was chosen to separate the groups. In several other studies a TT within 10 days was likewise considered "early".[23,24,26]

Two crises of the same patient were assumed to be separate from one another if the patient's status at discharge of the first crisis matched their pre-hospital status and additional triggers for the following crisis were identified.

Data Acquisition

Data on baseline demographics, clinical information, medication and comorbidities were obtained through medical charts

Table 1. Characteristics of Study Group.

Myasthenic crisis (n)	215
Patients (n)	193
Age (y)	67.1 ± 16.1 (14-89)
Male / Female	127 / 88
Rate of tracheostomy	107 (49.8%)

Age is depicted as mean ± SD and range.

Table 2. Tracheostomy.

Surgical / Dilatational tracheostomy	46 / 60 (1 unknown)
Days between intubation and tracheostomy	10.8 ± 6.2 (1-28)
Days between intubation and surgical / dilatational tracheostomy	12.1 ± 6.2 / 9.5 ± 5.8
Days of mechanical ventilation after tracheostomy	24.0 ± 25.8 (1-195)
Tracheostoma being removed before discharge	16 (15.0%)

"Days between intubation and tracheostomy" and "Days of mechanical ventilation after tracheostomy" are mean ± Standard Deviation and range. "Days between intubation and surgical / dilatational tracheostomy" is mean ± Standard Deviation.

and institutional databases. Characteristics reviewed included antibody-status, evidence of thymoma, thymectomy, Myasthenia Gravis Foundation of America (MGFA)- Score prior to MC and previous MGFA-Score if documented. Assessed treatment regimens were IVIG, PE, immunoadsorption (IA), use of intravenous pyridostigmine and continuous potassium infusion. We recorded, moreover, whether or not TT was performed, time between intubation and TT, number of days of mechanical ventilation after TT, removal of tracheostoma before discharge and TT during a previous crisis. Analyzed data regarding the clinical course of the crisis included ICU-LOS and hospital-LOS and duration of MV. Duration of MV was given in days; a day was counted as MV even if the patients had just MV for a few hours. Non-invasive ventilation (NIV) after extubation was also taken into account in days of MV. The number of days of MV presented in this manuscript are the days at ICU, not including days of MV when patients were transferred to rehabilitation clinics still needing MV.

Statistics

GraphPad Prism 5® (GraphPad Software, La Jolla, USA) was used for statistical analysis. Data was presented as mean (standard deviation and range). Group-comparison was tested with either student-t test or Chi-square test, respectively. The significance level was set to both-sided. For comparison of time of TT with days of mechanical ventilation at ICU, days at ICU and days in hospital Spearman's rank correlation was used.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Local ethic committees and institutional review boards of the participating centers approved the study based on the central vote of the ethics committee at University of Regensburg (No: 15-101-0259).

Consent for Publication

Not applicable.

Data Availability

Anonymized data will be made available upon reasonable request.

Results

Characteristics of Study Group and Tracheostomy

The patient cohort consisted of 215 MCs in 193 different patients, as 17 patients were included with more than one crisis (Table 1). In 107 (49.8%) of cases physicians decided to perform TT. TT was performed slightly more often in percutaneous dilatational technique (56.6%) (Table 2) rather than surgical. The median period of time between intubation and TT was 10 days (rang 1-28, mean 10.8 ± 6.2). The mean duration of MV after TT was 24 days (24.0 ± 25.8). In 15.0% (n = 16) of patients the tracheostoma was closed before discharge from ICU.

Differences in Tracheostomized vs. Non Tracheostomized Patients

Comparing the baseline characteristics and features of MC of patients with or without TT, there were a few significant differences: The frequency of early-onset MG (27 vs 12, $p = 0.01$) and the rate of thymus hyperplasia (8 vs 1, $p = 0.04$) were significantly higher in non tracheostomized patients (Table 3). Of note, 1 patient with thymus hyperplasia, who was tracheostomized had their thymectomy after MC; in the remaining 8 patients with thymectomy prior to MC, extubation was possible. Patients without TT were more likely to have been living at home, either independently or dependent on help (74 [68.5%] vs 66 [61.7.%]), and less likely to have been staying in a care facility or hospital before the crisis (25 [23.1%] vs 35 [32.7%]) (Table 3). In terms of clinical characteristics, tracheostomized patients during MC had a higher prevalence of multiple concurrent chronic diseases (20 [18.7%] vs 9 [8.3%], $p = 0.03$) and comorbidities such as diabetes mellitus (34 [31.8%] vs 21 [19.4%], $p = 0.04$). The mean number of MV days (34.4 ± 27.7 [range 2-219] versus 7.9 ± 7.8 [range 1-64], $p < 0.0001$), ICU length of stay (ICU-LOS) (34.8 days ± 25.5 [range 2-219] versus 12.1 ± 8.0 [range 1-49], $p < 0.0001$) and days in hospital (40.7 days ± 26 .7 [range 9-219] versus 22.6 ± 11.7 [range

Table 3. Characteristics of Patients With or Without Tracheostomy.

Myasthenic crisis	Tracheostomy (n = 107)	No Tracheostomy (n = 108)	P-value
Age	67.9 ± 15.7 (17-89)	64.4 ± 17.1 (14-84)	0.12
Male / Female	68 / 39	59 / 49	0.21
BMI	27.9 ± 10.5 (14-67.6)	27.1 ± 7.7 (17.3-58.4)	0.66
Extreme BMI (<16 or >40)	6 (14.3%)	2 (4.5%)	0.15
Pulmonary disease	23 (21.5%)	26 (24.1%)	0.75
Heart disease	46 (43%)	40 (37.0%)	0.41
Diabetes mellitus	**34 (31.8%)**	**21 (19.4%)**	**0.04**
Tumor (other than Thymoma)	14 (13.1%)	16 (14.8%)	0.84
Dialysis	1 (0.9%)	2 (1,9%)	1.0
Smoker	11 (10.3%)	6 (5,6%)	0.22
Alcohol addicted	5 (4,7%)	3 (2,8%)	0.50
≥ 3 diseases (Kidney, Heart, Lung, Diabetes, Tumor)	**20 (18.7%)**	**9 (8.3%)**	**0.03**
Myasthenia gravis			
Antibody status			
AchR-AB	90 (84.1%)	92 (85.2%)	
MusK-AB	9 (8.4%)	10 (9.3%)	n.s.
Titin-AB	21 (19.6%)	21 (19.4%)	
Seronegativ	7 (6.5%)	7 (6.5%)	
Early-onset	**12 (11.5%; 3 unknown)**	**27 (25.2%; 1 unknown)**	**0.01**
Paraneoplastic MG	32 (29.9%)	30 (27.8%)	0.76
Thymus hyperplasia	**1 (0.9%)**	**8 (7.4%)**	**0.04**
MGFA-classification before crisis			
First manifestation of MG	25 (23.4%)	22 (20.4%)	
Class I	7 (6.5%)	6 (5.6%)	
Class II	24 (22.5%)	31 (28.7%)	
Class III	29 (27.1%)	29 (26.9%)	
Class IV	14 (13.1%)	14 (12.9%)	n.s.
Unknown	8 (7.5%)	6 (5.6%)	
Status before crisis			
Independent at home	**44 (41.1%)**	**63 (58.3%)**	
At home dependent on help	**22 (20.6%)**	**11 (10.2%)**	**0.01**
In a care facility or hospital	**35 (32.7%)**	**25 (23.1%)**	
Unknown	**6 (5.6%)**	**9 (8.3%)**	
Myasthenic crisis			
Cause of crisis			
Infection	58 (54.2%)	54 (50%)	
First episode	25 (23.4%)	22 (20.4%)	n.s.
Poor treatment compliance	10 (9.3%)	11 (10.2%)	
Idiopathic/unknown	19 (17.6%)	25 (23.1%)	
Outcome			
Days of mechanical ventilation at ICU	**34.4 ± 27.7 (2-219)**	**7.9 ± 7.8 (1-64)**	**<0.0001**
Days at ICU	**34.8 ± 25.5 (2-219)**	**12.1 ± 8.0 (1-49)**	**<0.0001**
Days in hospital	**40.7 ± 26.7 (9-219)**	**22.6 ± 11.7 (2-66)**	**<0.0001**
Death	10 (9.3%)	18 (16.7%)	0.16
Therapy			
IVIG	**68 (63.6%)**	**50 (46.3%)**	**0.01**
Plasmaexchange / Immunadsorption	57 (53.3%)	53 (49.1%)	0.06
IVIG + Plasmaexchange or Immunadsorption	**28 (26.2%)**	**13 (12%)**	**0.009**
continuous pyridostigmine infusion	52 (48.6%)	43 (39.8%)	0.22
continuous potassium infusion	**69 (64.5%)**	**41 (38%)**	**0.0001**

Comparison of 107 patients in tracheostomy group and 108 patients in non- tracheostomy group. Age, "Days of mech. ventilation at ICU", "Days at ICU" and "Days in hospital" are mean ± Standard Deviation and range, other parameters are total number with percentage in brackets. AB = antibody, AchR = acetylcholine receptor, BMI = body mass index, ICU = intensive care unit, IVIG = intravenous immunoglobulin, MGFA = Myasthenia Gravis Foundation, MusK = muscle-specific receptor tyrosine kinase, n.s. = not significant. T-test was used for statistical analysis of age-differences and for comparison of "Days of mech. ventilation at ICU", "Days at ICU" and "Days in hospital". For other parameters Chi-square test was used. Significant differences are given in bold.

2-66], $p < 0.0001$) were significantly higher (Table 3) in patients requiring TT. Treatment regimens of MC differed between the participating centers. In general, the treatment of patients with TT was more aggressive: Mono-Therapy with IVIG and the combination of IVIG and PE / IA were chosen slightly more often in patients of the TT-group (n = 28 vs 13, p = 0.009), as was continuous potassium infusion (n = 69 vs 41, p = 0.0001) compared to the non-TT group.

Early Tracheostomy Is Associated With Shorter Duration of Mechanical Ventilation at ICU and Shorter ICU-LOS

Fourteen of 107 tracheostomized patients had to be excluded, as 10 died in hospital and 4 patients had already been tracheostomized or intubated before admission to the participating centers and/or data of the exact duration of ventilation was missing. A moderate correlation was found between the timing of TT and the number of days needing MV at ICU and ICU-LOS (r = 0.54, $p < 0.0001$) and a weak correlation to the number of days in hospital (r = 0.38) (Figure 1). To minimize the bias of the correlation analysis by confounders favoring shorter duration of MV and ICU-stay in MC, we compared patients with TT within 10 days of intubation to TT that were performed after 10 days (Table 4). The mean time to TT was 6 days (6.0 $\pm$ 2.7 [range 1-10]) in the early TT group (n = 48) and 16 days (16.0 $\pm$ 4.6 [range 11-28]) in the late TT group (n = 45) ($p < 0.0001$) (Table 4). Patients with TT within 10 days were slightly younger (68.4 $\pm$ 16.6 versus 71.7 $\pm$ 12.0, p = 0.04). No further significant differences were found between the groups (Table 4). Known factors associated with a longer time of MV at ICU in patients with MC (diabetes mellitus, multiple ($\geq$ 3) chronic diseases, late-onset MG as well as cardiopulmonal resuscitation (CPR) and pneumonia)[9] did not differ significantly (Table 4). Despite small differences in the patients' characteristics, the mean duration of MV at ICU (26.2 days $\pm$ 18.1 [range 5-101] versus 42.0 $\pm$ 33.1 [range 13-219], p = 0.006), ICU-LOS (26.2 days $\pm$ 14.6 [range 8-87] versus 42.3 $\pm$ 33.0 [range 13-219], p = 0.003) and days in hospital 33.0 $\pm$ 18.2 [range 9-87] versus 45.4 $\pm$ 32.2 [range 17-219], p = 0.03) were significantly shorter in the early TT group (Table 4).

Of all tracheostomized patients, 38 (40.9%) were discharged to a weaning facility. Patients in the late TT group needed MV more likely when discharged (n = 23, 51.1%) compared to the early TT group (n = 15, 31.3%) (p = 0.0515).

Discussion

The main findings of our study were: a) Half of the patients were tracheostomized in MC. b) Patients with TT had less often early-onset MG and were more likely to have multiple chronic diseases. c) Early TT was associated with a significant decrease in the duration of MV at ICU, ICU-LOS and hospital-LOS as well as a trend to be less often ventilator dependent at discharge.

Previous studies analyzing ventilator-dependent critically ill patients had very diverse findings regarding the rate of TT. In cohorts including unselected critically ill patients the rate of TT ranged between 7-43%.[16,31-35] Neurocritical care patients with diseases of the CNS showed a TT rate of 7-35 %.[31,34,36-38] Two preceding studies on TT in patients with MC found that 8 of 13 (61.5%) [39] and 9 of 23 (39%) intubated MC patients were tracheostomized.[40] In our large cohort 49.8% of 215 MCs underwent TT. This data suggests that patients during MC requiring MV are more often in need of TT than other critically ill patients. This could be explained by the combination of neuromuscular disease with respiratory insufficiency and dysphagia and the high risk of extubation failure.[15,16,18,41] Except late-onset MG, we could not find any MG-specific risk factors for TT, but the treatment regimens during MC in the TT group were more aggressive. This may reflect a more severe course of MC.

In ventilated neurological ICU patients, favorable effects were seen when comparing early with late TT or prolonged endotracheal intubation, which is in concordance with our findings. In a retrospective cohort-study of 1,154 patients with severe traumatic brain injury, early TT (within 8 days) was associated with reduced duration of MV, shorter ICU-LOS and hospital-LOS and fewer VAP compared to late TT. [25,42-44] However, a randomized controlled trial in 60 patients with severe stroke, did not demonstrate any differences in ICU-LOS between early and late TT groups, but the need of sedation and the mortality rate, were significantly reduced after early TT.[22] Other studies demonstrated inconclusive results as well.[25,26,45,46]

In cohorts of mixed critical ill patients studies showed a higher ventilation tolerance, effectiveness of bronchial toilet, reduced risk of VAP, accelerated weaning from mechanical ventilation as well as shorter ICU-LOS,[19-21,42] while others found no benefits for early TT.[26-29]

Weaning patients with MG is often challenging. Extubation failures is common in MC (27-44%) which has been associated with longer ICU-LOS and time in hospital[15,16,18] as well as prolonged duration of MV and higher incidence of VAP.[16] Thus, the effect of early tracheostomy might be explained simply through elimination of extubation failure in patients which were tracheostomized without extubation attempt.

In a recent study we evaluated demographics and baseline characteristics of patients with MC. Comorbidity, late-onset MG, status and higher MGFA-Score prior to the crisis and complications during MC as pneumonia and CPR were associated with an extended duration of MV.[9] In the present study none of these factors showed to be significantly different between the early and late TT group, showing that the conditions for the weaning were similar in both groups.

A reduction in ICU-LOS,[25,43,46,47] days of MV[19,42-44,46] and hospital-stay-LOS[10,21,25,43] in other NICU populations was likewise found to be the case with our patients: early timing of TT correlated with fewer days of ventilatory support at ICU and ICU-LOS with an average reduction of 16 days respectively. This difference was surprisingly high and might not

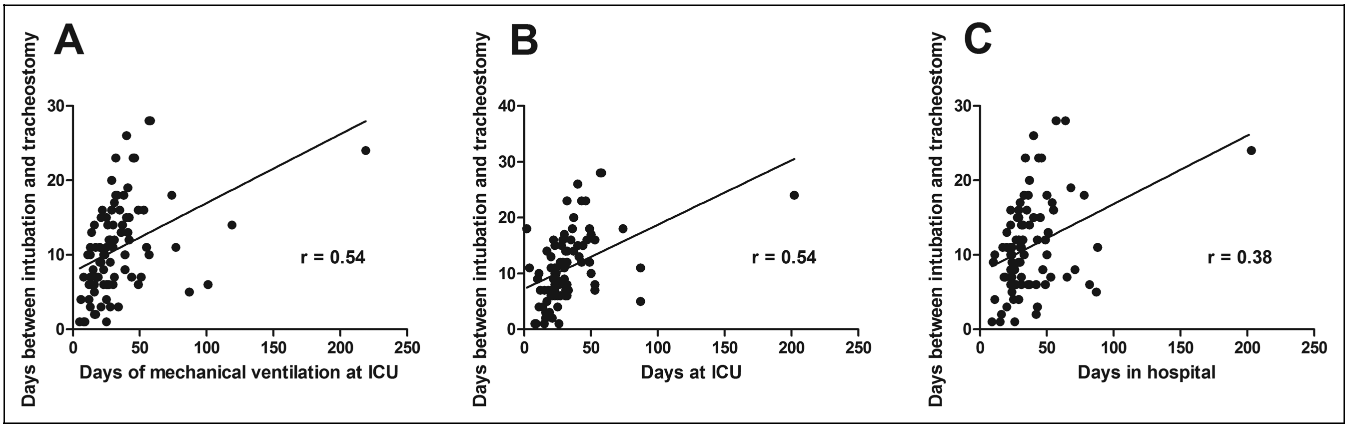

Figure 1. Correlations between the time point of the tracheostomy and outcome (A) "Days between intubation and tracheostomy" and "Days of mechanical ventilation at ICU" of each patient are depicted as black dots. (B) "Days between intubation and tracheostomy" and "Days at ICU" of each patient are depicted as black dots. (C) "Days between intubation and tracheostomy" and "Days in hospital" of each patient are depicted as black dots. (A-B) Time point of tracheostomy correlated moderate with "Days of mechanical ventilation at ICU" and "Days on ICU" (R = 0.54; Spearman's rank correlation), (C) the correlation with "Days in hospital" was weak (R = 0.38; Spearman's rank correlation).

Table 4. Characteristics of Patients With Tracheostomy Within or After 10 Days.

Patients	Tracheostomy ≤10 days (n = 48)	Tracheostomy >10 days (n = 45)	P-value
Age	**68.4 ± 16.6 (17-89)**	**71.1 ± 12.0 (37-87)**	**0.04**
Male / Female	30 / 18	26 / 19	0.68
BMI	29.0 ± 12.2 (14-67.6)	27.5 ± 8.9 (18.8-54.3)	0.67
Extreme BMI (<16 or >40)	4 (16.0%)	2 (11.1%)	1.0
Heart disease	17 (35.4%)	20 (44.4%)	0.4
Diabetes mellitus	15 (31.3%)	16 (35.6%)	0.67
≥ 3 diseases (Kidney, Heart, Lung, Diabetes, Tumor)	9 (18.8%)	8 (17.8%)	1.0
Early-onset	7 (14.6%; 2 unknown)	4 (8.9%; 1 unknown)	0.52
MGFA-classification before crisis			
First manifestation of MG	15 (31.3%)	8 (17.8%)	
Class I	3 (6.3%)	3 (6.7%)	0.15 for First
Class II	12 (25.0%)	11 (24,5%)	episodes
Class III	9 (18.8%)	14 (31,1%)	
Class IV	7 (14.6%)	6 (13.3%)	1.0 for Rest
Unknown	2 (4.2%)	3 (6.7%)	
Status before crisis			
Independent at home	26 (54.2%)	18 (40.0%)	
At home dependent on help	11 (22.9%)	10 (22.2%)	
In a care facility or hospital	9 (18.8%)	14 (31.1%)	n.s.
Unknown	2 (4.2%)	3 (6.7%)	
Complications			
Pneumonia	34 (70.8%)	33 (73.3%)	0.82
CPR	4 (8.3%)	7 (15.6%)	0.35
Outcome			
Day of mech. ventilation before tracheostomy	**6.0 ± 2.7 (1-10)**	**16.0 ± 4.6 (11-28)**	**<0.0001**
Days of mech. ventilation at ICU	**26.2 ± 18.1 (5-101)**	**42.0 ± 33.1 (13-219)**	**0.006**
Days at ICU	**26.2 ± 14.6 (8-87)**	**42.3 ± 33.0 (13-219)**	**0.003**
Days in hospital	**33.0 ± 18.2 (9-87)**	**45.4 ± 32.2 (17-219)**	**0.03**

Comparison of 48 patients, where tracheostomy was performed within 10 days to 45 patients with tracheostomy after 10 days of mechanical ventilation. Age, "Days of mech. ventilation at ICU", "Days at ICU" and "Days in hospital" are depicted as mean ± SD and range, other parameters in total number with percentage in brackets. BMI = body mass index, CPR = Cardio-pulmonal resuscitation, ICU = intensive care unit, MGFA = Myasthenia Gravis Foundation, n.s. = not significant. T-test and Chi-square test were used, where appropriate. Significant differences are given in bold.

simply be due to the earlier timing of the TT. Especially, the reduced need of drugs like sedatives and antibiotics that might worsen MC could explain some of the favorable effects of early TT. [48-51] The easier management of aspiration after TT in MCs with hypersalivation due to cholinergic drugs might also contribute to these results. Moreover, TT reduces the volume of the anatomical dead space and facilitates breathing, which might be an important factor especially in patients with neuromuscular diseases. Patients with MC have no central nervous system disturbance and wake up more quickly after termination of sedatives than other neurointensive care patients and therefore can benefit from weaning, training and physiotherapy after early TT. In addition, early TT enables patients to be transferred to rehabilitation and weaning clinics at an earlier time point which is another advantage. Of note, in our study early TT seemed to reduce the likelihood of ventilator dependency when discharged to a weaning facility (31% versus 51%), supporting the theory that patients benefit from an early TT.

All in all, we are of the opinion that an early TT in patients in MC requiring MV should be considered to reduce the ventilation time and ICU-LOS, if prolonged weaning is predictable.

Our study has several limitations: The definite number of days of MV is unknown in some patients because of the transfer to rehabilitation and weaning facilities while still mechanically ventilated. The decision which patient to tracheostomize early was a subjective decision by the clinician in charge. The aim of a clinician is to identify patients in need of prolonged invasive ventilation as they benefit from early TT. If patients with a good short time prognosis were chosen for the early TT, the effect of the early TT might be overestimated. Finally, because of the retrospective nature, certain clinical data might be inaccurate. Therefore, a prospective randomized controlled trial including ventilation data to evaluate the exact effect of early TT in MC is required.

Conclusion

In summary, we found a high rate (49.8%) of TT in patients with MC. Factors associated with TT were older age, a late-onset MG and a higher number of comorbidities. In patients requiring prolonged mechanical ventilation, early TT was associated with a shorter duration of MV, as well as ICU and hospital-LOS and might be an additional therapeutic option in MC.

Abbreviations

AB	Antibody
AChR	Acetylcholine receptor
BMI	Body mass index
CPR	Cardiopulmonal resuscitation
hospital-LOS	Hospital length of stay
IA	Immunoadsorption
ICU	Intensiv Care Unit
ICU-LOS	ICU length of stay
IVIG	Intravenous immunoglobulins
MC	Myasthenic crisis
MG	Myasthenia gravis
MGFA	Myasthenia Gravis Foundation of America
MUSK	Muscle-specific kinase
MV	Mechanical ventilation
NICU	Neuro-Intensive Care Units
PE	Plasma exchange
SD	Standard deviation
TT	Tracheostomy
VAP	Ventilator-associated pneumonia.

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Contributions

Klemens Angstwurm MD and Amelie Vidal, These authors contributed equally to this work.

KA, AV and BN wrote the manuscript. HS, CD, PM, SK, SS, JB, UN, DHL, STG, HBH, AT, JD, CR, HS, ES, HR, HF, BB, IK, CSG, AA, JZ, BS, AS and AM revised the manuscript critically for important intellectual content. KA, AV and BN designed the study and the statistical analysis plan. AV and BN critically reviewed the study and the statistical analysis plan. BN and UN performed the statistical analysis. KA provided senior statistical support and critically reviewed the results of the statistical analysis. JB, AM, BB, CSG, AV, HS, CD, PM, SK, SS, DHL, STG, HBH, AT, JD, CR, HS, ES, HF, BB, IK, AA, JZ, BS, AS provided all the data and contributed substantially to the conception and design of the study. All authors read and approved the final manuscript. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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References

1. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. *Lancet Neurol*. 2015;14(10):1023-1036.
2. Melzer N, Ruck T, Fuhr P, et al. Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the guidelines of the German neurological society. *J Neurol*. 2016;263(8):1473-1494. Accessed March 16, 2016.
3. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *Lancet. Neurol*. 2009;8(5):475-490.
4. Phillips LH 2nd. The epidemiology of myasthenia gravis. *Ann NY Acad Sci*. 2003;998(1):407-412.
5. Fink ME. Treatment of the critically ill patient with myasthenia gravis. In: Ropper AH (ed) *Neurological and Neurosurgical Intensive Care*, 3rd edn. Raven Press, 1993:351-362.
6. Thomas CE, Mayer SA, Gungor Y, et al. Myasthenic crisis: clinical features, mortality, complications, and risk factors for prolonged intubation. *Neurology*. 1997;48(5):1253-1260.
7. Alshekhlee A, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. *Neurology*. 2009;72(18):1548-1554.
8. Bedlack RS, Sanders DB. On the concept of myasthenic crisis. *J Clin Neuromuscul Disease*. 2002;4(1):40-42. Accessed June 9, 2016. http://ovidsp.tx.ovid.com/ovftpdfs/FPDDNCLBMCMBGJ00/fs027/ovft/live/gv008/00131402/00131402-200209000-00009.pdf
9. Neumann B, Angstwurm K, Mergenthaler P, et al. Group for the German myasthenic crisis study. myasthenic crisis demanding mechanical ventilation: a multicenter analysis of 250 cases. *Neurology*. 2020;94(3):e299-e313. https://n.neurology.org/content/neurology/early/2019/12/04/WNL.0000000000008688.full.pdf
10. Ramos-Fransi A, Rojas-García R, Segovia S, et al. Myasthenia gravis: descriptive analysis of life-threatening events in a recent nationwide registry. *Eur J Neurol*. 2015;22(7):1056-1061.
11. Ronager J, Ravnborg M, Hermansen I, Vorstrup S. Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis. *Artifi Organs*. 2001;25(12):967-973.
12. Gajdos P, Chevert S, Clair B, Tranchant C, Chastang C.Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. myasthenia gravis clinical study. *Ann Neurol*. 1997;41(6):789-796.
13. Gold R, Krenzer M, Klinker E, et al. Efficacy and safety of immunoadsorption vs plasmapheresis vs combination for treatment of myasthenic crisis: comparative retrospective study on 72 patients. *Neurology*. 2008;70(11):A427-A427.
14. Anderson CD, Bartscher JF, Scripko PD, et al. Neurologic examination and extubation outcome in the neurocritical care unit. *Neurocritical Care*. 2011;15(3):490-497.
15. Seneviratne J, Mandrekar J, Wijdicks EFM, Rabinstein AA. Predictors of extubation failure in myasthenic crisis. *Arch Neurol*. 2008;65(7):929-933.
16. Wu J-Y, Kuo P-H, Fan P-C, Wu H-D, Shih F-Y, Yang P-C. The role of non-invasive ventilation and factors predicting extubation outcome in myasthenic crisis. *Neurocrit Care*. 2009;10(1):35-42. Accessed March 18, 2016.
17. Liu Z, Yao S, Zhou Q, et al. Predictors of extubation outcomes following myasthenic crisis. *J Int Med Res*. 2016;44(6):1524-1533.
18. Rabinstein AA, Mueller-Kronast N. Risk of extubation failure in patients with myasthenic crisis. *Neurocrit Care*. 2005;3(3):213-215.
19. MacIntyre NR. Evidence-based guidelines for weaning and discontinuing ventilatory support. *Chest*. 2001;120(6):375-395. Accessed October 12, 2016.
20. van der Lely AJ, Veelo DP, Dongelmans DA, et al. Time to wean after tracheotomy differs among subgroups of critically ill patients: retrospective analysis in a mixed medical/surgical intensive care unit. *Respir Care*. 2006;51(12):1408-1415.
21. Griffiths J, Barber VS, Morgan L, Young JD. Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. *BMJ (Clinical Research Ed.)*. 2005;330(7502):1243.
22. Bosel J, Schiller P, Hook Y, et al. Stroke-related early tracheostomy versus prolonged orotracheal intubation in neurocritical care trial (setpoint): a randomized pilot trial. *Stroke*. 2012;44(1):21-28.

23. Rumbak MJ, Newton M, Truncale T, Schwartz SW, Adams JW, Hazard PB. A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. *Crit Care Med*. 2004;32(8):1689-1694.
24. Andriolo BNG, Andriolo RB, Saconato H, Atallah ÁN, Valente O. Early versus late tracheostomy for critically ill patients. *Cochrane Database Syst Rev*. 2015;60(1):91.
25. Rabinstein AA, Wijdicks EFM. Outcome of survivors of acute stroke who require prolonged ventilatory assistance and tracheostomy. *Cerebrovas Dis (Basel, Switzerland)*. 2004;18(4):325-331. Accessed July 23, 2018. https://sslgate.uni-regensburg.de/Article/Pdf/,DanaInfo=www.karger.com,SSL+80771
26. Gomes Silva BN, Andriolo RB, Saconato H, Atallah AN, Valente O. Early versus late tracheostomy for critically ill patients. *Cochrane Database Syst Rev*. 2012;(3):CD007271.
27. Blot F, Similowski T, Trouillet J-L, et al. Early tracheotomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. *Intensive Care Med*. 2008;34(10):1779-1787.
28. Trouillet J-L, Luyt C-E, Guiguet M, et al. Early percutaneous tracheotomy versus prolonged intubation of mechanically ventilated patients after cardiac surgery: a randomized trial. *Ann Inter Med*. 2011;154(6):373-383.
29. Terragni PP, Antonelli M, Fumagalli R, et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. *JAMA*. 2010;303(15):1483-1489.
30. Deutschen Gesellschaft für Neurologie. Diagnostik und therapie der myasthenia gravis und des lambert-eaton-syndroms– leitlinien für diagnostik und therapie in der neurologie. 2017. Accessed October 19, 2010. https://dgn.org/leitlinien/ll-68-ll-diagnostik-und-therapie-der-myasthenia-gravis-und-des-lambert-eaton-syndroms/
31. Alsherbini K, Goyal N, Metter EJ, et al. Predictors for tracheostomy with external validation of the stroke-related early tracheostomy score (SETscore). *Neurocritical Care*. 2019;30(1):185-192.
32. Goettler CE, Fugo JR, Bard MR, et al. Predicting the need for early tracheostomy: a multifactorial analysis of 992 intubated trauma patients. *J Trauma*. 2006;60(5):991-996.
33. Sanabria A, Gómez X, Vega V, Domínguez LC, Osorio C. Prediction of prolonged mechanical ventilation in patients in the intensive care unit: a cohort study. *Colombia Med (Cali, Colombia)*. 2013;44(3):184-188.
34. Steidl C, Bösel J, Suntrup-Krueger S, et al. Tracheostomy, extubation, reintubation: airway management decisions in intubated stroke patients. *Cerebrovasc Dis (Basel, Switzerland)*. 2017;44(1-2):1-9.
35. Arabi YM, Alhashemi JA, Tamim HM, et al. The impact of time to tracheostomy on mechanical ventilation duration, length of stay, and mortality in intensive care unit patients. *J Crit Care*. 2009;24(3):435-440. doi:10.1016/j.jcrc.2008.07.001. Epub January 17, 2009. Accessed September 28, 2016. https://www.ncbi.nlm.nih.gov/pubmed/19327302
36. Van der Lely AJ, Veelo DP, Dongelmans DA, Korevaar JC, Vroom MB, Schultz MJ. Time to wean after tracheotomy differs among subgroups of critically ill patients: retrospective analysis in a mixed medical/surgical intensive care unit. *Respir Care*. 2006;51(12):1408-1415.
37. Qureshi AI, Suarez JI, Parekh PD, Bhardwaj A. Prediction and timing of tracheostomy in patients with infratentorial lesions requiring mechanical ventilatory support. *Crit Care Med*. 2000;28(5):1383-1387.
38. Ali MI, Fernández-Pérez ER, Pendem S, Brown DR, Wijdicks EFM, Gajic O. Mechanical ventilation in patients with Guillain-Barré syndrome. *Respir Care*. 2006;51(12):1403-1407. http://rc.rcjournal.com/content/respcare/51/12/1403.full.pdf
39. Werneck LC, Scola RH, Germiniani FM, Comerlato EA, Cunha FM. Myasthenic crisis: report of 24 cases. *Arquivos de Neuro-Psiquiatria*. 2002;60(3A):519-526. Accessed March 14, 2016. http://www.scielo.br/pdf/anp/v60n3A/11118.pdf
40. O'Riordan JI, Miller DH, Mottershead JP, Hirsch NP, Howard RS. The management and outcome of patients with myasthenia gravis treated acutely in a neurological intensive care unit. *Eur J Neurol*. 1998;5(2):137-142.
41. Rabinstein AA, Wijdicks EFM. Weaning from the ventilator using BiPAP in myasthenia gravis. *Muscle & Nerve*. 2003;27(2):252-253.
42. Bouderka MA, Fakhir B, Bouaggad A, Hmamouchi B, Hamoudi D, Harti A. Early tracheostomy versus prolonged endotracheal intubation in severe head injury. *J Trauma*. 2004;57(2):251-254.
43. Alali AS, Scales DC, Fowler RA, et al. Tracheostomy timing in traumatic brain injury: a propensity-matched cohort study. *J Trauma Acute Care Surg*. 2014;76(1):70-76; discussion 76-8.
44. Teoh WH, Goh KY, Chan C. The role of early tracheostomy in critically ill neurosurgical patients. *Ann Acad Med Singap*. 2001;30(3):234-238.
45. Do Valle Pinheiro B, de Oliveira Tostes R, Brum CI, et al. Early versus late tracheostomy in patients with acute severe brain injury. *J Bras Pneumol*. 2010;36(1):84-91.
46. Dunham CM, Cutrona AF, Gruber BS, Calderon JE, Ransom KJ, Flowers LL. Early tracheostomy in severe traumatic brain injury: evidence for decreased mechanical ventilation and increased hospital mortality. *Int J Burn Trauma*. 2014;4(1):14-24.
47. Ahmed N, Kuo Y-H. Early versus late tracheostomy in patients with severe traumatic head injury. *Surg Infect*. 2007;8(3):343-347.
48. Wang SH, Xie YC, Jiang B, et al. Fluoroquinolone associated myasthenia gravis exacerbation: clinical analysis of 9 cases. *Zhonghua Yi Xue Za Zhi*. 2013;93(17):1283-1286.
49. Perrot X, Bernard N, Vial C, et al. Myasthenia gravis exacerbation or unmasking associated with telithromycin treatment. *Neurology*. 2006;67(12):2256-2258.
50. Jones SC, Sorbello A, Boucher RM. Fluoroquinolone-associated myasthenia gravis exacerbation: evaluation of postmarketing reports from the US FDA adverse event reporting system and a literature review. *Drug Saf*. 2011;34(10):839-847.
51. Rossi M, Lusini G, Biasella A, Mazzocchio R. Prulifloxacin as a trigger of myasthenia gravis. *J Neurol Sci*. 2009;280(1-2):109-110.