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Predictors of Prolonged Duration of Mechanical Ventilation and Mortality in Patients with Guillian-Barre Syndrome

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Background: Nearly one-third of the patients with Guillian-Barre syndrome (GBS) require ventilatory assistance, the duration of which is variable. There are no studies from India to predict the duration of ventilatory requirement in patients with GBS which might help direct the clinician to perform a tracheostomy. **Aim**: To study the predictors that determine the duration of mechanical ventilation (MV) and the outcome of GBS patients requiring MV. **Materials and Methods**: This is a retrospective, observational study from a referral teaching hospital. All consecutive patients diagnosed with GBS and requiring mechanical ventilation between 2009-2018 were included in the study. The demographic, clinical parameters, electrophysiological data, complications and outcome of these patients was noted. Factors predicting prolonged MV (>2 weeks) were statistically assessed. **Result**: Out of 79 patients requiring MV, 45(57%) patients needed prolonged MV and tracheostomy was performed in 29(37%). On multivariate regression analysis, sepsis (p=0.02; {95%CI 1.3-24.4}), MRC sum score (p=0.01; {95% CI 0.89-0.99}) and lower albumin levels on day 14(p=0.004{95% CI 0.05-0.57}) correlated with prolonged duration of MV. On univariate analysis, axonal variant of GBS(p=0.02), presence of chronic renal disease(p=0.03) and pulmonary disease(p=0.01) were associated with significant mortality. On multivariate regression analysis, age (>60 years) (p=0.001) {95% CI 0.89-0.97}, prolonged duration of MV(p=0.02) {95%CI 0.88-0.99}, MRC sum score(p=0.01) {95% CI 1.01-1.1} correlated with poor outcome. **Conclusions**: Sepsis and septic shock and not the choice of immunotherapy nor the electrophysiological subtypes of GBS determined the prolonged duration of MV in our cohort, though the axonal variant on electrophysiology predicted the mortality.

Keywords: Guillain Barre syndrome, Mechanical ventilation, Sepsis

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Introduction

Guillian- Barre syndrome (GBS) is an acute and fulminant inflammatory polyradiculoneuropathy that presents as progressive weakness of limbs with generalised areflexia or hyporeflexia. Most patients require hospitalisation, and in about 30 % of the cases, ventilator assistance is needed during their illness [1]. Some patients show a quick recovery, while some require prolonged mechanical ventilation (MV) (a requirement for MV for more than two weeks) due to worsening bulbar and respiratory muscle weakness or due to the respiratory complications inherent to prolonged immobility [2]. Previous studies have attempted to identify simple, functional markers to predict prolonged MV, which can help the critical care team plan an early tracheostomy [3,4]. To date, there are no studies in India on patients with GBS on prolonged MV. Here, we aimed to identify the predictive factors determining the duration and outcome of patients with GBS requiring prolonged MV.

Patients and Methods

This study was conducted in a tertiary care referral hospital over eight years (2009-2018). This was a retrospective and observational study. Any patient with a diagnosis of GBS and requiring mechanical ventilation were included in the study. Those with incomplete data or those who left against medical advice were excluded. The diagnosis of GBS was based on the electrodiagnostic criteria laid by Ho et al. [5]. The demographic data, muscle power grading according to the medical research council (MRC) scale, presence of facial & bulbar weakness and associated co-morbid conditions such as hypertension, diabetes and chronic kidney disease (CKD) were noted. The severity of the disease was assessed by Hughes disability status scale. The MRC sum score was obtained and was stratified into three groups (0-20, 21-40 and 41-60) to compare with the outcome [6]. The ventilator requirement includes the mode {invasive or non-invasive/ continuous positive airway pressure (CPAP), synchronised intermittent mechanical ventilation (SIMV) or assist controlled mode (ACV)}, the duration of ventilation and total duration of hospital stay were noted. The timing and the complications related to percutaneous tracheostomy was noted.

Electrophysiological studies were conducted (by Medtronic key point) at admission, day seven and third week of their illness.

The parameters included distal latency, conduction velocity, combined motor action potentials (CMAPs) and F wave latency, sensory nerve action potential amplitude (SNAP) and sensory nerve conduction velocity of two upper limbs and two lower limbs nerves.

Patients with GBS were subtyped electrophysiologically based on Ho's criteria into acute motor axonal neuropathy (AMAN)/acute motor-sensory axonal neuropathy (AMSAN)/ demyelinating polyneuropathy (AIDP) or unexcitable nerves (taking the last nerve conduction study at the third week of the illness). Dysautonomia was defined as unexplained fluctuations in heart rate of (>30 bpm) or systolic /diastolic blood pressure fluctuations (>30/15 mmHg or significant bowel or bladder dysfunction [7,8]. The presence of sepsis and septic shock was based on the third international consensus definition of sepsis and septic shock [9,10]. Cerebrospinal fluid analysis (CSF) for albumin-cytological dissociation, serum albumin levels at baseline, day 14, albumin transfusion were recorded.

The outcome was grouped as either death or improvement by more than one grade on Hughes functional grading scale. The follow-up details were obtained through the case record data when patients visited for follow up at 3 and 6 months.

Statistical analysis: Duration of mechanical ventilation and the outcome at discharge was the main outcome variable. Age, Gender, MRC sum score, presence of comorbidities were explanatory variables. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. The association between categorical explanatory variables and the quantitative outcome was assessed by comparing the mean values. An independent sample t-test was used to assess statistical significance. The association between explanatory variables and categorical outcomes was assessed by cross-tabulation and comparison of percentages. The Chi-square test was used to test statistical significance. P-value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

Results

Seventy-nine patients required MV out of 224 patients admitted during the study period (Table 1). The median age of the patients was 42 years (2 to

77 years). The average duration of disease was six days (range 0-22 days). The mean admission single breath count was 14, while the mean single breath count at the intubation time was 10. The mean duration of hospital stay from admission was 27 days (3-68 days), while the duration of ventilator requirement from time of intubation was 17 days (1-50 days). Treatment with IVIG or plasma exchange was given within 0-2 days of admission in Hughes grade 4-5. The therapy received was IVIG in 56 patients and PLEX in 22, while one patient did not opt for any treatment due to financial constraints but still improved.

Table 1: Baseline and explanatory parameters of the study population (79 patients).

Parameter	Frequency	Percent
1. Age groups		
<=40	39	49.37%
41-60	28	35.44%
>60	12	15.19%
II.Gender		
Male	52	65.82%
Female	27	34.18%
III.MRC sum score		
41-60	8	10.13%
21-40	38	48.10%
0-20	33	41.77%
Diabetes mellitus	12	15.2%
Hypertension	14	17.7%
Smoking	28	35.4%
Chronic kidney injury	3	3.8%
Pulmonary disease	29	36.7%
Sepsis	40	50.6%
Shock	20	25.3%
Urinary tract infection	12	15.2%
Bedsore	8	10.1%

The baseline parameters of the patients were mentioned as percentages.

The indication of MV was progressive respiratory muscle weakness in 71(90%) patients, followed by pneumonia in 6(8%) and cardiac failure with pulmonary oedema in 2(3%) patients. Only 29(37%) patients needed tracheostomy. Sepsis and septic shock were the parameters that determined the timing of tracheostomy($p<0.01$). Neither age, gender, single breath count, facial, bulbar weakness, MRC sum score nor diabetes, hypertension nor smoking indicated a need for tracheostomy. Seventeen (22%) patients had dysautonomia during their hospital stay.

Eight patients had fluctuations in the blood pressure of greater than 30/15 mmHg (with swings between hypertensive episodes to hypotension). Two patients had persistent hypotension requiring inotrope support. Temporary pacemaker insertion was seen in 7 (8.8%) patients due to tachy-bradyarrhythmia. Hyponatremia due to SIADH was seen in 19 (24%) patients but did not contribute to the prognosis.

Electro physiologically, there were 42(53%) patients with AIDP, 25(32%) with axonal GBS (AMAN/AMSAN), and in 12(15%) patients, the nerves were unexcitable (Table2).

Table 2: Association of Ventilation duration with ENMG of the study population (N=79

ENMG	Ventilation duration		Chi-Square Value	P-value
	Normal (N=34)	Prolonged ventilation (N=45)		
AMAN	5 (29.41%)	12 (70.59%)	1.81	0.612
ASMAN	4 (50%)	4 (50%)		
AIDP	20 (47.62%)	22 (52.38%)		
Indeterminate	5 (41.67%)	7 (58.33%)		

The table shows the association between the electrophysiological subtypes of GBS and the prolonged duration of ventilation. None of the subtypes determined the long duration of mechanical ventilation.

Seven (1%) patients could be managed for a short period on CPAP ventilation mode alone while immunotherapy was being administered. One patient had single lung ventilation due to lung resection for severe pre-existing lung disease. Serum albumin level was less than 3g/dl in 45(57%) patients on follow up (within day 14), with normal levels (>3.5g/dl) at admission suggesting a huge catabolic state. Eighteen (23%) patients received at least one albumin transfusion during the hospital stay independent of the status of plasma exchange. In this study, there were 45(57%) patients who needed prolonged MV, while 34(43%) needed a shorter duration of ventilation. None of the parameters like age($p=0.50$), gender($p=0.77$), facial($p=0.92$) & bulbar weakness($p=0.32$), single breath count($p=0.12$) and smoking($p=0.27$) correlated with the need for prolonged MV (Table 5). Similarly, comorbidities like diabetes($p=0.25$) or hypertension($p=0.24$) did not determine the need for a stay on a ventilator beyond 14 days. Duration of hospital stay was in direct proportion with a duration of MV($p=0.01$).

Even the MRC scores of the individual muscles (Table 4) did not correlate with the duration of MV.

Table 3: Association of MRC sum scores (at the peak of the illness) with ventilation duration in study population (N=79)

	Ventilation duration		P-value (Mann Whitney U- test)
	Less than two weeks (N=34)	More than two weeks (N=45)	
MRC1 NECK	2 (1.75,3)	2(1,3)	0.34
MRC DELTOID	2(1,3)	2(0,3)	0.27
MRC BICEPS	2 (1,3)	2(0.5,3)	0.37
MRC ECR2	2 (1,3)	2(1,3)	0.29
MRC ILIOPSOAS	2 (1,3)	2(1,3)	0.21
MRC QUADRICEPS	2 (1,3)	2(1,3)	0.19
MRC TA3	2 (1,3)	2(1,3)	0.15
MRC SUM SCORE	24 (12,38)	24 (9,36)	0.16

Abbreviations: MRC1=Medical research council, ECR2=Extensor carpi radialis TA3=Tibialis anterior

The power of the individual muscle groups did not correlate with the prolonged duration of mechanical ventilation. Twelve (27 %) patients with AMAN, 4(9%) of AMSAN, 22(49%) of patients with AIDP and 7(16%) with unexcitable nerves had received prolonged MV (Table 2). These electrophysiological subtypes did not determine the duration of MV(p=0.612). However, on multivariate regression analysis, sepsis (p=0.02; {95%CI 1.3-24.4}), MRC sum score (p=0.01; {95% CI 0.89-0.99}) and albumin levels within day 14(p=0.004{95% CI 0.05-0.57}) correlated with prolonged duration of MV. Severe weakness in lower MRC sum score (less than 20) predicted high mortality during hospital stay(p=0.007). CKD and pulmonary disease were the other important parameters that predicted significant mortality (p=0.03 and 0.01, respectively). Clinical parameters such as bulbar weakness(p=0.31), single breath count(p=0.76), diabetes(p=0.17), hypertension(p=0.43), smoking(p=0.75) were not statistically significant as predictors of outcome (Table 4).

Table 4: Association of outcome with Demographic parameters of the study population (N=79)

Demographic parameters	Outcome at discharge		P-value
	Death (N=32)	Improved (N=47)	
Age N (%)			
<=40	11 (34.37%)	28 (59.57%)	0.08
41-60	14 (43.75%)	14 (29.78%)	
>60	7 (21.87%)	5 (10.63%)	
Gender N (%)			
Male	19 (59.37%)	33 (70.21%)	0.32
Female	13 (40.62%)	14 (29.78%)	
Bulbar Mean ± SD	0.63±0.66	0.49±0.51	0.31
MRC sum score N (%)			
41-60	3 (9.375%)	5 (10.63%)	0.007
21-40	9 (28.12%)	29 (61.70%)	
0-20	20 (62.5%)	13 (27.65%)	
Diabetes mellitus	7 (21.9%)	5 (10.6%)	0.17
Hypertension	7 (21.9%)	7 (14.9%)	0.43
Pneumonia	17 (53.1%)	12 (25.5%)	0.01
Smoking	12 (37.5%)	16 (34%)	0.75
Chronic kidney disease	3 (9.4%)	0 (0%)	0.03
Sepsis	19 (59.4%)	21 (44.7%)	0.20
Shock	11 (34.4%)	9 (19.1%)	0.13
Duration of stay In days (mean +_SD)	31.69±18.42	23.91±12.88	0.03

Parameters such as lower MRC sum score, pneumonia and chronic kidney disease and prolonged duration for the hospital stay correlated with mortality. Axonal GBS was present in 56% of the patients who died while demyelinating pattern on electrophysiology was seen in 27%(p=0.02). On multivariate regression analysis, age (>60 years) (p=0.001) {95% CI 0.89-0.97}, duration of MV(p=0.02) {95%CI 0.88-0.99}, MRC sum score(p=0.01) {95% CI 1.01-1.1} correlated with poor outcome.

Out of the patients who died, 23 (72%) patients needed a prolonged duration of MV, while only nine (28%) needed a shorter course(p=0.01). Overall, the most common cause of mortality in these patients was sepsis and septic shock (65%). The frequently identified organisms in culture-positive sepsis (in the blood/tracheal aspirate or the urine) were Acinetobacter baumanii, Pseudomonas aeruginosa, Serratia marcescens, methicillin-resistant staphylococcus aureus and candida Albicans. The other causes adding to the mortality were dysautonomia 17(22%), CKD (6%), pulmonary thromboembolism (3%). At three months of follow up, two more patients expired after discharge-one due to sudden cardiac death of unknown cause and another due to myocardial infarction. There were no deaths during the 3-6 month follow up period.

Nine (20%) out of 45 surviving patients improved during the first three months, while 14 patients (39%) enhanced during three to six months' time frame to an ambulatory status, i.e., they were able to walk a distance of 5 metres with a walker or support (Hughes grade 3).

The improvement within six months of follow up did not correlate to their duration of mechanical ventilation (p=0.34).

Discussion

The number of patients who required MV (35%) was similar to the other studies [11]. The common indicators of MV were respiratory muscle weakness and pneumonia [12,13]. A previous study showed that the combination of single breath count, neck weakness and bulbar symptoms was an excellent bedside predictor of the need for MV [14]. The average single breath count in our study was ten, and it was a significant clinical indicator for intubation.

The defining duration for prolonged mechanical ventilation in critically ill patients is variable, some authors quoting two weeks, three weeks and two months [4,15,16]. Conventionally, we took two weeks, which was felt more practical indicator of the need for tracheostomy. The anticipation of the duration of MV enables the clinician to plan the right time for tracheostomy. Only 37% of the patients underwent tracheostomy, which was a low rate [4]. This difference reflects a practice parameter, allowing an uncomplicated and improving patient to stretch for a few more days rather than performing an early tracheostomy. The significant predictor for tracheostomy was again sepsis, and the complications were rare and hence unlikely to have influenced the outcome.

The most common cause of death in our study was sepsis, septic shock and pneumonia. The mortality in other studies is between 1 -18% [17]. Ours being a tertiary referral hospital, there could have been a possible referral bias. Deaths in these patients occurred predominantly during the critical care unit stay that required intensive ventilator care. Nearly 18% of the patients were still non-ambulatory at six months, similar to other studies (18).

Sepsis and septic shock were 'the' important parameters that determined the duration of mechanical ventilation and the need for tracheostomy. A study from the Netherlands of 150 patients with mechanical ventilation showed that patients with weakness of deltoid muscles with MRC score of 0-2; those with unexcitable nerves or axonopathy on electrophysiology had a greater chance of prolonged duration of MV and probably early tracheostomy might be indicated in them [4].

Another study proposed foot flexion weakness after immunotherapy as a simple, functional marker for prolonged MV [3]. Early tracheostomy or not "–is dependent on several systemic and practice parameters and not GBS and neurological parameters alone [19,20]. In our study, the duration of mechanical ventilation was not dependant on the electrophysiological subtypes(p=0.5), MRC scores of the individual muscles, nor the therapy they received. Axonal GBS or AIDP did not predict when the patient would be on a ventilator, but an uncomplicated GBS patient might make an early recovery. In other words, if GBS patients are supported with adequate sepsis control measures, nutritional care and judicial antibiotic treatment, they might tolerate a wean off from the ventilator independent of the clinic-electrophysiological parameters of GBS nor the immunotherapy they received [21]. Mortality in our study was directly associated with the duration of hospital stay(p=0.03) and axonopathy in electrophysiological studies (p=0.02). Elderly individuals had a greater risk attributed to their coexistent comorbidity [21].

Fluctuations in blood pressure predict cardiac arrest [22,23,24]. Our patients with dysautonomia had severe fluctuations in blood pressure necessitating inotropes and short-acting antihypertensive drugs for shock and hypertensive crisis, respectively. Fluctuations in heart rate were managed with temporary cardiac pacing. Some patients had vagal supersensitivity, causing heart rate fluctuations, particularly during manoeuvres such as endotracheal suctioning. The dysautonomia in our patients was diagnosed after carefully excluding sepsis which can mimic similar clinical features.

Conclusions

GBS is a self-limiting disease with a natural course of progression followed by recovery. Unlike the Western literature, sepsis was a significant determinant of the duration of MV and tracheostomy. Sepsis control and good supportive care are more crucial in shortening the ventilatory period, thereby obviating the need for tracheostomy.

What this study adds to the existing knowledge

Though western studies have shown that the MRC score of the deltoid muscle, and an axonal variant of

GBS on electrophysiology, determined the prolonged duration of mechanical ventilation, this study showed the predictors of prolonged duration of mechanical ventilation were sepsis and septic shock. This highlights that GBS has a natural recovery course independent of electrophysiological subtype, and measures should be taken to prevent and treat sepsis.

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