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Characteristics of Therapeutic Plasma Exchange Procedures in Patients with Myasthenia Gravis and Guillain Barre Syndrome and their Outcomes during Hospitalization in General Intensive Care Unit Hasan Sadikin General Hospital Bandung in January 2017 to December 2020

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Abstract

Background: Myasthenia Gravis and Guillain-Barré syndrome are two of the most common autoimmune diseases affecting the peripheral nervous system in the world. Both of the diseases manifested as progressive muscle weakness, areflexia, and inspiratory muscle weakness which leads to mechanical ventilation support. Therapeutic Plasma Exchange is the first line of treatment according to the American Society for Apheresis (AFSA), which is a relatively safe and often performed procedure In the Intensive Care Unit (ICU), including in Hasan Sadikin Hospital Bandung (RSHS). **Purpose:** The goal of this study is to obtain the background characteristics of MG and GBS patients and to obtain the outcome of TPE in these patients. **Methods:** The study was a descriptive study performed on 30 MG and GBS patients who received TPE in the Intensive care unit, RSHS from January 2017 to December 2020. Data for the study was obtained retrospectively from the patient medical record. **Results:** The result showed that the most common side effect during TPE was electrolyte imbalance. There was no reported morbidity and mortality in MG patients, in contrast to two mortality cases in GBS patients. Length of stay in the intensive care unit was influenced by several factors including age, comorbidities, the severity of MG, and morbidities that occurred during the hospital stay. **Conclusion:** Outcome of MG and GBS patients with TPE procedure is good in relation with low TPE-unrelated morbidity and mortality.

Keywords: Guillain Barre Syndrome, Length of Stay, Myasthenia Gravis, Morbidity, Mortality, Therapeutic Plasma Exchange

1. Introduction

Myasthenia Gravis (MG) and Guillain-Barré syndrome (GBS) are the most common autoimmune diseases affecting the peripheral nervous system. The incidence of MG in Europe is estimated at 30 from 1 million people per year with male-female ratio of 1:3 (Aydin et al., 2017). The worldwide incidence of GBS is 1.3–4 from 100.000 cases annually and is more common in young adults and older adults (>50 years) with male-female ratio of 3:1.^{3–5} Currently, there is no particular registered data regarding MG and GBS in Indonesia (Murthy et al., 2020; Biswas et al., 2020; Ortiz-Salas et al., 2016).

Myasthenia gravis is an autoimmune disease characterized by the presence of antibodies to the acetylcholine nicotinic postsynaptic receptor accompanied by fluctuating muscle weakness. MG is a progressive disease with a high mortality, estimated to be around 5% to 9%. Approximately, 3-8% of patients who experience a *Myasthenia gravis crisis* will die from this condition (Westerberg et al., 2020). The other disease investigated in this study was Guillain-Barré syndrome (GBS). GBS is an autoimmune disease of the peripheral nervous system that causes progressive muscle weakness and areflexia. The disease is characterized by acute neuromuscular paralysis that ends in respiratory failure and approximately 25% of patients require mechanical ventilation (Nguyen et al., 2012).

Diseases of MG and GBS are the most often conditions indicated to receive TPE therapy in the GICU RSUP Dr. Hasan Sadikin Bandung. Following the guidelines recommended by the American Society for Apheresis (ASFA), the first-line treatment of MG, especially acute phase MG, and GBS crisis is the administration of TPE (McCullough et al., 2019; Li et al., 2018). Therapeutic Plasma Exchange (TPE) procedure uses an extracorporeal technique in which blood plasma is separated from other blood components and exchanged with fluids replacement.⁹ The purpose of TPE is removal of toxins present in patient's plasma. Based on research in the United States, TPE has performed as many as 1200 procedures per year and another study reported TPE procedures accounted for 76.8% of the total *therapeutic apheresis*. Regardless, Indonesia has not done a specific study that describes the number of TPE procedures carried out each year (Pham et al., 2019).

Procedure of TPE is generally safe and well-tolerated, though, complications are not evitable. Complications include hemodynamic instability, coagulation disorders, electrolyte disturbances, allergic reactions (pruritus, urticaria and anaphylactic reactions), hematomas at the catheter insertion site, and acute myocardial infarction (Daga Ruiz et al., 2017). Complications, along with the onset of TPE implementation, frequency, and type of fluid replacement are considered to affect the outcomes of patient (Calca et al., 2020).

Several factors that can also contribute to the patient's outcome are the severity of the disease, comorbidities, and precipitating factors. Assessment of patient outcomes was described on the duration of ventilator usage, morbidity, mortality, and length of stay in the GICU as well as the total length of stay in the hospital. Eventhough TPE is a routine procedure that has long been carried out in the GICU Dr. Hasan Sadikin Bandung, there is no data regarding the implementation of TPE and its outcomes for patients. Therefore, this study aims to obtain an overview of the characteristics of MG and GBS patients and to find out the outcomes of implementing the TPE procedure for the diseases.

2. Method

This study used a descriptive method with retrospective data collection. The research subjects were medical records of patients of MG and GBS who had underwent TPE at GICU Dr. Hasan Sadikin Bandung from January 2017 to December 2020. Inclusion criteria were medical records of patients aged 18 years and over, were intubated and using a ventilator while undergoing TPE in the GICU. The exclusion criteria were incomplete patient medical records. The sample size was determined based on the data availability (*purposive sampling*). This research was conducted at RSUP Dr. Hasan Sadikin Bandung in November – December 2021 after obtaining approval from the Research Ethics Committee.

The variables in this study include patient characteristics, characteristics of TPE procedures, complications of TPE procedures, and patient outcomes. Patient characteristics include gender, age, body mass index, comorbidities,

precipitating factors, APACHE II, and MG class. The characteristics of the TPE procedure include the onset, frequency, and type of fluid replacement. Complications of the TPE procedure include hemodynamic disturbances, electrolyte disturbances, impaired coagulation factors, allergic reactions, paraesthesia, hematomas in venous access, and *myocardial infarction*. Patient outcomes included length of use of a ventilator, morbidity, mortality, length of stay in the GICU, and length of stay in hospital.

The collected data were then analyzed using descriptive statistics. The data processing was done using statistical software (Microsoft® Excel 2019 and IBM SPSS 25.0) and displayed in tables. For categorical data (nominal) would be presented in frequency and percentage statistics, while for numerical data (ordinal, interval) would be presented in the average value, standard deviation, median value, minimum value and maximum value.

3. Results

3.1 Data Normality Test

During the study period, there were 48 MG and GBS patients who were treated at the GICU Hasan Sadikin Hospital. Twenty one patients belonged to the MG group with only 19 patients met the criteria of inclusion and exclusion and 19 patients belonged to the GBS with only 11 patients met the criteria of inclusion and exclusion.

The data in this study underwent normality test. Numerical data was tested with Shapiro Wilks because the number of data is less than 50. Table 4.1 describes the results of the normality test for the distribution of this research data. The results of the normality test showed normal distribution of data when the p value in the *Shapiro Wilk test* was more than 0.05.

Table 1: Result of data normality test

Variable	MG (n = 19)		GBS (n = 11)	
	P value	Data distribution	P value	Data distribution
Age	0,225	Normal	0,361	Normal
Body mass index	0,019	Odd	0,001	Odd
APACHE II	0,006	Odd	0,083	Normal
Onset (days)	0,000	Odd	0,164	Normal
TPE frequency	0,000	Odd	0,000	Odd
Duration of Ventilator use	0,017	Odd	0,143	Normal
Length of stay GICU	0,003	Odd	0,011	Odd
Length of stay RSHS	0,016	Odd	0,009	Odd

Normality test using *Shapiro Wilk* (n<50) method, data were declared normally distributed if p-value > 0.05

3.2 Characteristics of Patients

Characteristics of MG and GBS patients in this study included mean age, number of women and men, median body mass index, number of patients with comorbidities, number of patients with comorbid factors precipitating factors, and median and mean APACHE II scores. MG patients were classified according to the MG class.

Table 2: Characteristics of research subjects (n=30)

Characteristics of patients	MG (n = 19)	GBS (n = 11)
a. Age		
Mean (SD)	43,47 (13,94)	34,09 (10,51)
b. Gender		
Male	7 (36,8%)	6 (54,5%)

	Female	12 (63,2%)	5 (45,5%)
c.	Body mass index		
	Median (Q1 - Q3)	20,81 (18,73 - 23,44)	22,89 (22,04 - 24,22)
d.	Comorbid		
	Yes	12 (63,2%)	7 (63,6%)
	No	7 (36,8%)	4 (36,4%)
e.	Precipitating factos		
	Yes	4 (21,1%)	6 (54,5%)
	No	15 (78,9%)	5 (45,5%)
f.	APACHE II		
	Mean (SD)		14,18 (7,39)
	Median (Q1 - Q3)	9 (5 - 16)	
g.	<i>Myasthenia Gravis</i> class		
	II	8 (42,1%)	0 (0%)
	IIIb	11 (57,9%)	0(0%)

3.3 Characteristics of TPE Procedure

This study obtained a description of TPE procedure characteristics which included median onset in MG subjects and mean onset in GBS subjects, and data on the number of TPE procedures on subjects and the median. As additional data, was discovered that days of improvement in ventilator mode were found in the median of third cycle in both groups of subjects.

Table 3: Characteristics of TPE procedure

TPE Procedure	MG (n = 19)	GBS (n = 11)
a. Onset (days)		
Mean (SD)	-	5,05 (1,43)
Median (Min - Max)	6 (1 - 29)	-
b. Frecuency		
Number of actions (times)	96	58
Median (Min - Max)	6 (2 - 6)	6 (1 - 6)
c. Improvement of the ventilator mode (cycle)		
Median (Min-Max)	3 (1 - 4)	3 (2 - 4)

Furthermore, this study describes the type of fluid replacement in the implementation of TPE. Plasmanate, NaCl 0.9%, Ringer's Lactate, Gelofusine, Fresh Frozen Plasma (FFP) and albumin 4-5% are the types of fluids used in this study. Plasmanate consists of albumin and globulin so that albumin is then included in the plasmanate group.

Table 4: Overview and comparison of the use of replacement fluid

Fluids	MG (n = 19)	GBS (n = 11)
a. Plasmanat/Albumin 5%	96 (100%)	58 (100%)
b. NaCl 0,9%	63 (65,6%)	53 (91,4%)
c. Ringer Laktat	5 (5,2%)	3 (5,2%)
d. Gelofusine	96 (100%)	58 (100%)
e. FFP	0 (0%)	0 (0%)

3.4 Complications of TPE Procedure

Complications that occurred during the TPE procedure in the MG group were mostly hypocalcemia and the least was hemodynamic disturbances, namely hypotension. Overall, the total complications in the MG group were 56 events. Total complications in the GBS group occurred in 33 events.

Table 5: Overview and comparison of complications during TPE

Complications	MG (n = 19)	GBS (n = 11)
Hemodynamic disturbances		
a. Hypotension	1 (1%)	2 (3,4%)
b. Electrolyte imbalances		
Hiponatremia	20 (20,8%)	16 (27,6%)
Hipokalemia	12 (12,5%)	13 (22,4%)
Hipocalcemia	32 (33,3%)	12 (20,7%)
c. Coagulation disorders	6 (6,3%)	5 (8,6%)
d. Etc	0 (0%)	0 (0%)
e. Total complications	56 (58,3%)	33 (56,9%)

3.5 Overview of Patients Outcomes

This study obtained a description of the outcome of patients undergoing TPE in each group. The outcome domains studied in this study were length of ventilator use, morbidity; associated and unrelated TPE, mortality; related and unrelated to TPE, length of stay in GICU, and the length of hospital stay.

Table 6: Overview and comparison of patients outcomes

Patients outcomes	MG (n = 19)	GBS (n = 11)
a. Length of ventilator use		
Mean (SD)		10,18 (7,72)
Median (Min-Max)	7 (1 - 23)	
b. Morbidity		
TPE associated	0 (0%)	0 (0%)
TPE unrelated	10 (52,6%)	6 (54,5%)
c. Mortality		
TPE associated	0 (0%)	2 (18,2%)
TPE unrelated	1 (5,3%)	0 (0%)
d. Length of stay		
GICU		
Mean (SD)	13,26 (8,94)	14,64 (11,21)
Median (Min-Max)	11 (4 - 42)	12 (2 - 41)
Hospital		
Mean (SD)	24,74 (13,02)	27,73 (21,66)
Median (Min-Max)	21 (7 - 62)	21 (5 - 74)

4. Discussion

The patients of MG and GBS has mean age of 43.5 years old and 34.1 years old. Previous research stated that MG is a disease that affects all ages (Bubuioc et al., 2021). Another study reported that the incidence of GBS increases with age but it may be due to the difficulty of diagnosing GBS at a younger age (Sejvar et al., 2011).

Epidemiological reports for the Chinese region stated the proportion of women more than men by 3:1 in MG patients. MG is an autoimmune disease and the disease has been associated to be more common in women. The effect of the hormone estrogen is considered as one of the mediators causing differences in autoimmune women and men. A study conducted on the epidemiology of GBS stated that GBS occurs more often in men than women. The male predominance in GBS differs from most other autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus, which often show higher rates in women (Dong et al., 2020).

Among the patients of MG, 2 of them had BMI of 30 kg/m². Obesity in MG patients were assessed as being directly proportional to the presence of comorbidities and the incidence of complications during the TPE procedure. Hypoxia and systemic inflammation that occur in high BMI patients have poor effect on patients' outcomes and could trigger MG crisis (Liu et al., 2017). In the GBS group, there were 2 patients with BMI > 30kg/m² (obese) and 1 patient with BMI >25kg/m² (overweight). A cohort study investigating the relationship between BMI and hip circumference with the incidence of GBS revealed positive result. However, another cohort study in Denmark found that BMI was not associated with the risk of developing GBS. This is similar to our study where the mean BMI was normal in GBS subjects but this may be due to the limited number of subjects, making it difficult to describe the overall incidence rate (Winer et al., 2014).

This study found that the most comorbid in MG patients were pulmonary TB in as many as 5 people. A study in Taipei, Taiwan stated that the incidence of pulmonary TB was significantly higher in MG patients in association to immunosuppressant therapy which made them susceptible to exposures of active pulmonary TB infection, and most pulmonary TB infections triggered exacerbations in MG cases. Comorbidity in GBS patients was found in 7 people, of which 3 patients suffered from hypertension, 3 patients from obesity, and 1 patient with *Chronic Inflammatory Demyelinating Polyneuropathy* (CIDP). The presence of comorbidities in the patient affects the outcome and length of treatment (Ou et al., 2013).

Precipitating factors for MG in this study were found in 3 of 19 patients with upper respiratory tract infections. The unknown precipitating factors of the other patients was possibly due to incomplete anamnesis in the medical record. The precipitating factors in the GBS group consisted of 5 GBS patients triggered by upper respiratory tract infections and 1 patient triggered by enteritis et causa suspect dysentery. Infection with *C. jejuni* is known to most often trigger GBS because the bacteria has a ganglioside-like structure in its lipopolysaccharide layer (Sejvar et al., 2011).

In the MG group, patients were in APACHE II median 9 (5-16). In the GBS subject group, the APACHE II score averaged 14.18 ± 7.39 SD. The APACHE II assessment in this study is only to describe in general the severity and mortality rate when patients enter the GICU which is influenced by the conditions and comorbidities suffered by the patient.

The MG patients in this study was found the most in Myasthenia Gravis class IIIb, as much as 57.9% of the total patients. This is because this study focuses on MG patients who are treated in the ICU and receive TPE therapy during their treatment so that most of the patients enter with symptoms of respiratory problems that require mechanical ventilation assistance.

We found that in the MG group, the TPE procedure onset was at a median of 6 days. In the GBS group, onset was at a mean of 5.05 days. Until present, there has been no study that states the optimal onset of TPE procedures in MG and GBS crisis patients, but a study conducted in Florida stated that after a person has diagnosed with acute phase MG or GBS crisis, immediate treatment is needed in the intensive care room.

The administration of TPE with a median frequency of 6 times in this study was carried out based on recommendations from the ASFA which stated that patients with severe MG could receive TPE 5 to 7 times, while GBS patients could receive TPE up to five times or more. This administration is carried out according to the clinical condition of the patient and must be evaluated after the first and second TPE administration (Pham et al., 2019).

The replacement fluids mostly used in the 96 performed TPE procedures were mostly plasmanate/albumin 5%, gelofusine 100%, and NaCl 0.9% in both MG and GBS groups. Plasmanate is used concurrently with gelofusine. The MG management guidelines used in Indonesia (PERDOSSI 2018) state that the most commonly used replacement fluid is 4%-5% human albumin in physiological saline. One cycle of TPE in adults will remove 150 grams of plasma protein containing 110 grams of albumin and 24 grams of globulins to eliminate 1-2 grams of pathogenic substances. This is the reason for preferring plasmanate as a replacement fluid in TPE because plasmanate contains albumin as well as globulins (Hakim et al., 2019).

Of the 96 TPE procedures performed, it was found that at the beginning of TPE procedure, there were about 52 cases (54.3%) of hypotension, but after fluid management was given, hypotension could be managed in less than 15 minutes and there was only 1 incident (1%) of untreated hypotension complications. The patient with the hypotension had BMI value of 32 kg/m² that according to a previous study in America in 2021, there were difficulties in calculating replacement fluids for obese patients so they conduct a greater risk of hypotension (Babariya et al., 2021). In the GBS group, most complications were of electrolyte disturbances. These complications are relatively minor and can be overcome during or after TPE is performed. A study stated that the most common complications of TPE were hypocalcemia and hypomagnesemia due to side effects of using citrate in anticoagulants followed by hypothermia, transfusion reactions, fluid disturbances, electrolyte disturbances, bleeding due to hypofibrinogenemia and thrombocytopenia, hypotension, and gastrointestinal symptoms such as nausea and vomiting (Sergent et al., 2022).

We describe the outcome of MG and GBS patients who received the TPE procedure at several points, namely: duration of ventilator use, morbidity, mortality and length of stay in the GICU, and length of stay in the hospital. We divide the morbidity and mortality in 2 aspects, TPE-associated and TPE-unrelated.

The duration of ventilator use in MG patients had a median value of 7 days. Five patients were on *prolonged ventilator* with the longest duration of 23 days. A study conducted in Germany in 2020 stated that the median use of a ventilator was 12 days and *prolonged ventilation* (>15 days) were affected by age, MG onset, MG grade, and the patient's comorbidities before the onset of MG crisis (Neumann et al., 2020). In GBS subjects, the duration of ventilator use had a mean value of 10.18 days. According to a study conducted in Pakistan, the frequency of need for ventilators ranges from 19% to 43% accompanied by *prolonged ventilators* in cases of severe GBS. The need for ventilators is reported to be very high, reaching 81% in patients with poor prognoses (Siddiqui et al., 2019).

There was no TPE-associated morbidity within the procedure in the MG and GBS subject groups. In the MG group, 4 patients had morbidity due to HAP, 4 patients were due to CAP, and 2 patients had sepsis. A previous retrospective study conducted over 10 years in India stated that 50% of patients experienced some morbidity during the crisis phase of MG (Lal et al., 2013). In the GBS group, 6 patients had *Hospital-Acquired Pneumonia* (HAP). No morbidity caused by the TPE procedure was found in this study, indicating that the TPE procedure is a relatively safe procedure to perform.

The mortality in the MG group was found to be TPE-unrelated in a 69-year-old woman with comorbid DM and hypertension and APACHE II with MG class IIIB. The mortality rate was not as poor as a study conducted in 2013 in India with the mortality rate of 30%.²⁴ Mortality in the GBS group occurred in two patients with HAP. Both subjects were hypotensive and were given fluids and vasopressors but the hypotension was not treated so the patient fell into *cardiac arrest*. A study conducted in Australia stated that the mortality of GBS patients was greater in patients who used mechanical ventilation and had a high APACHE score (Portugal Rodríguez et al., 2015). TPE itself is a relatively safe procedure with minimal complications so it rarely causes life-threatening conditions.

This research has found that the length of stay in GICU and hospital is influenced by the condition of the patient at the time of initial admission to the hospital. It divides the explanation of treatment on the grounds that the treatment in the GICU focuses on respiratory problems while the total length of hospital stay may be due to other factors.

In this study, we found that overall patients' quality of life in GBS group were lower than MG group. This can be seen from the large comorbidities suffered by the patient (MG 63,2% / GBS 63,6%), precipitating factors (MG 21,1% / GBS 54,5%), APACHE II scoring (MG 12 / GBS 14,18), duration of ventilator use (MG 7 / GBS 10), TPE unrelated morbidity (MG 52,6% / GBS 54,5%), TPE-associated mortality (MG 0% / GBS 54,5%), length of stay in GICU (MG 11 / GBS 12), and length of stay in hospital (MG 21 / GBS 21). There has been no previous study that examined the quality of life comparison of MG and GBS patients, so further research is needed on this matter.

Limitations in this study were incomplete data sources from patient medical records such as myasthenia gravis class and complaints of complications that occurred during the TPE procedure which was not included and were not asked. Another limitation is that this study has a small sample size so that it cannot cover the whole data.

5. Conclusions

The group of MG patients who were given the TPE procedure at the GICU RSHS had the average characteristics of being of productive age, female sex, and normal BMI. The outcome of the TPE procedure in MG patients in the GICU RSHS is favorable, indicated by the absence of morbidity and mortality associated with the TPE procedure.

The dominance characteristics of GBS patients was male in the productive age range. The outcome of the TPE procedure in GBS patients in the GICU RSHS is good. Cases of mortality during the TPE procedure occurred in 2 patients, but this was related to the patient's unprime condition when the TPE procedure performed. TPE is a relatively safe procedure and is the most recommended treatment for MG and GBS treated in the GICU RSHS, especially in patients with severe clinical symptoms or exacerbating conditions.

Suggestions for RSHS are to carry out routine check-ups before and after TPE procedure to evaluate the magnitude of the complication rate, give a higher albumin concentration at the beginning of the TPE procedure to avoid high incidence of hypotension, complete the recording of data on precipitating factors during history taking and myasthenia gravis class on the medical record, and revise and add details of complications in the TPE report form. A study with a larger number of subjects is needed to obtain a more representative picture regarding the management of TPE for MG and GBS patients in RSHS.

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Declaration of Conflicting Interest

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