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Original Research Article.

The Clinical Outcome among the Patients of Guillain Barre Syndrome After Therapeutic Plasma Exchange: Critical Reassessment of Effectiveness at BSMMU

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ABSTRACT

Introduction: Guillain–Barré syndrome (GBS) is an acute monophasic paralyzing illness usually provoked by a preceding infection. Mainly intravenous immunoglobulin (IVIG) and plasmapheresis (PP)/plasma exchange (PE) are used to treat this disease where for developing country IVIG is not cost effective and suitable.

Objective: In this study our main goal is to evaluate the clinical Outcome among the Patients of Guillain Barre Syndrome after therapeutic plasma exchange.

Method: This open label randomized clinical control trial was carried out at Department of Transfusion Medicine of BSMMU, Dhaka from April 2017-December 2017.The patients who are candidate for IVIg will be enrolled. One group received TPE and other will be treated in the conventional manner and conducted as control.40 patients with the age range of 15 to 60 years admitted to Intensive care unit of BSMMU and referred to neurology Department of this hospital for performing TPE. All patients had clinical findings of Guillain-Barre syndrome (GBS) and/or GBS variants.

Results: During study it was observed that 4(20.0%) patients belonged to age 25-34 years, 35-44 years and 45-54 years respectively in TPE group and 35-44 years and 45-54 years respectively in IvIg group and direct costs of IVIg therapy are more than twice that of TPE. Also patient's condition started improving after three cycles of TPE with power in the upper limbs 4/5 and lower limbs 3/5.

Conclusion: It can be concluded that TPE appears to be a less expensive and most effective first-line therapy option for treatment of patients with GBS.

Keyword: Guillain–Barré Syndrome (GBS), Intravenous Immunoglobulin (IVIG), Therapeutic Plasma Exchange (TPE).

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INTRODUCTION

Guillain–Barré syndrome (GBS) is an autoimmune disease of the peripheral nervous system. About one-third of the patients with GBS will require mechanical ventilation, and most GBS-related deaths occur as a result of respiratory failure. The annual incidence of GBS is 0.4–4 per 100,000 all over the world. Men are more frequently affected than women.Many people who develop GBS have had a recent chest or intestinal infection that may cause an allergic attack on the nerves. Antibodies against the infection also target the nerves and cause GBS.[1,2] Treatment of GBS entails management of severely paralyzed patients with intensive care and ventilator support, and specific immunomodulation therapies that shorten the progressive course of GBS, presumably by limiting nerve damage. High-dose intravenous immunoglobulin (IVIG) and plasmapheresis (PP)/plasma exchange (PE)/therapeutic apheresis aid more rapid resolution of the disease. Intravenous immunoglobulin (IVIg) is a treatment in which antibodies from donated blood are injected into a person's vein whereas use of therapeutic plasma exchange (TPE) as a treatment modality proved out to be an effective treatment option in several neurological diseases. But In developing countries plasma-derived products (IVIG) are not easily available and affordable to all, TPE is a better option.

Plasma exchange is one of most effective treatment that has been proven to be superior to supportive treatment alone in Guillain-Barre syndrome. Consequently, plasma exchange should be regarded as the treatment against which new treatments, such as intravenous immunoglobulin, should be judged. In mild Guillain-Barre syndrome two sessions of plasma exchange are superior to none. Plasma exchange is more beneficial when started within seven days after disease onset rather than later, but was still beneficial in patients treated up to 30 days after disease onset.[4] In this study our main goal is to evaluate the clinical Outcome among the Patients of Guillain Barre Syndrome after therapeutic plasma exchange.

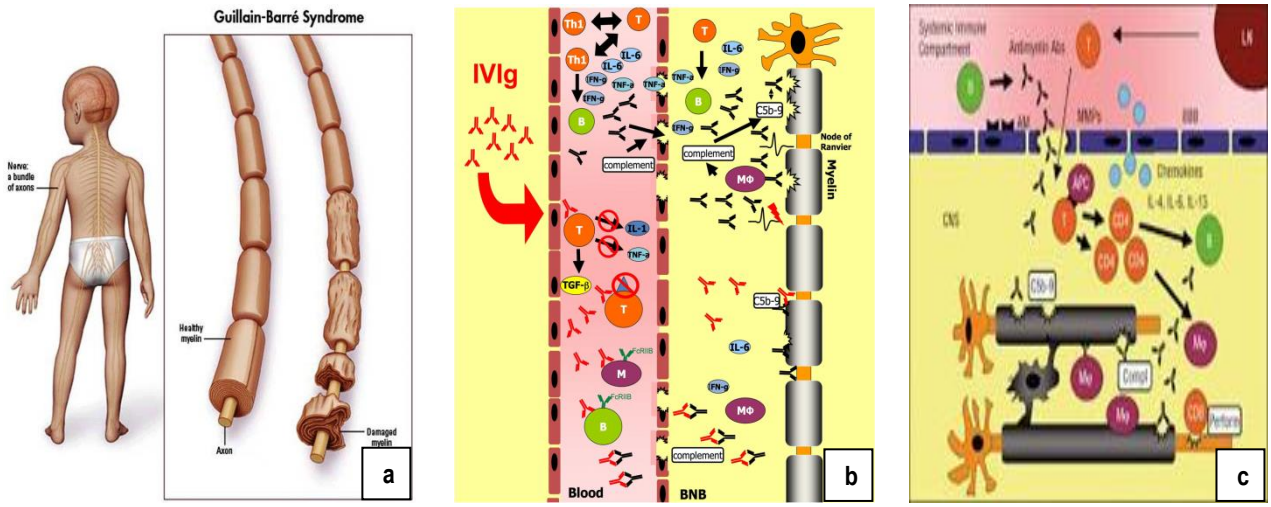

Figure 1a, 1b, 1c: Guillain–Barré syndrome (GBS) and its treatment (IVIG) and /plasma exchange (TPE) mechanism.[3]

OBJECTIVES

General Objective

- To estimate the clinical Outcome among the Patients of Guillain Barre Syndrome after therapeutic plasma exchange.

Specific Objective

- To identify antecedent event of the study patients.
- To observe improvement of the study patients after TPE and IVIG treatment.

METHODOLOGY

Study Type

Open label randomized clinical control trial.

Place and Period of Study

This study was conducted at Department of Transfusion Medicine of BSMMU, Dhaka from April 2017-December 2017.

Sample Size (n)

The patients who are candidate for IVIg will be enrolled. One group received TPE and other will be treated in the conventional manner and conducted as control. The simplest, approximate sample size formula for binary outcomes, assuming α = 0·05, power = 0·90, and equal sample sizes in the two groups.

n = the sample size in each of the groups

p1 = event rate in the treatment group (when R and p2 are estimated)

p2 = Event rate in the control group

R = Risk ratio (p1/p2)

Estimate a 30% event rate in the control group (p2 = 0·30) and determine that the clinically important difference to detect is a 35% improvement (R = 2.523) with the treatment (Clinical improvement 75.7% in their muscle strength in Therapeutic plasma exchange Shrivastava et al. (2015) at α = 0·05 and power = 0·90. (Note: R=2.523 equates to an event rate in the treatment group of p1 = 0·757, i.e., R = 75.7%/ 30%)

p1 = 0.757

p2 = 0.30

R = 2.523

n = 19.82

=20 in each group

Therefore 40 (20 x 2 = 40) sample will be enrolled in this study

Inclusion Criteria

- 15 to 60 years of male and female GBS
- Progressive weakness of variable degree from mild paresis to complete paralysis.
- Generalized hypo- or areflexia,
- Demonstration of relative limb asymmetry regarding paresis.
- Mild to moderate sensory signs.
- Patients who will not develop respiratory muscle paralysis.
- Patients who will be selected for IVIg (Ropper, 2005)
- a. Adult (age 15-60) b. Acute onset c. Progressive
- Autonomic dysfunction includes tachycardia, other arrhythmias, postural hypotension, hypertension, and other vasomotor symptoms.
- Gastrointestinal illness (e.g., diarrhea),
- PT, APTT, INR, serum albumin, serum calcium – within normal physiological limit.
- Cerebrospinal fluid (CSF) showing elevated CSF protein, CSF cell counts <10 mononuclear cell/mm3.

Exclusion Criteria

- Severely deteriorated patients
- Severe Anemia

Method

In this randomized clinical trial, 40 patients with the age range of 15 to 60 years admitted to Intensive care unit of BSMMU and referred to neurology Department of this hospital for performing TPE and its evaluation, from May 2016 to December 2017.

Among them 20 patients will receive therapeutic plasma exchange and 20 patients will receive conventional medical treatment (IVIG) by the lottery method. All patients had clinical findings of Guillain-Barre syndrome (GBS) and/or GBS variants. TPE procedures will performed on haemonatics apheresis machine (Manufacturer) on an alternate day using a double lumen femoral catheter depending on the clinical condition of the patient. A minimum of 1 and maximum of 10 cycles of plasma exchange will performed depending upon the clinical outcome in the patient. Calcium gluconate infusion (10 ml of calcium gluconate in 500 ml normal saline [NS]) will give during the procedure to prevent citrate toxicity. Acid citrate dextrose: Whole blood ratio used was 1:10, blood flow rate was kept between 25 and 40 ml/min depending on the weight of the patient and blood volume of the patient will calculated. Depending on the amount of plasma exchange, the duration of procedure varied from 1 to 1.5 h. The TPE kit was primed first with NS and then with group specific, screened, and cross-matched packed red blood cells for patients who had weight <25 kg to avoid hypoxia and hypovolemia. Patient's total blood volume was calculated as per Nadler's formula and processed through central double lumen catheter. 1-1.5 times plasma volume was exchanged with NS and fresh frozen plasma (FFP) to prevent hypotension. The ratio of NS and FFP for replacement fluid was 1:1.

Continuous monitoring of vitals, e.g., pulse, blood pressure and respiratory rate was carried out during the procedure to prevent any adverse events related to the procedure. Details of the procedural complications, if any, were noted and analyzed. Pre- and post-procedure coagulation parameters along with hematological parameters were done at every procedure. Clinical improvement was assessed by measuring the grading of muscle power and functional grading scales as per Medical Research Council Scales before and after completion of TPE schedule. Intravenous immunoglobulin (IVIG) is preferable in children weighing <15 kg. Steroids are not used as a treatment protocol.

Data Analysis

Statistical analysis will be carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). It will be a randomized clinical control trial. Here two group will be taken, one will be case group and another will be control. The analysis will be done MRC and MMT examination and some lab investigations. The mean values will be calculated for continuous variables. The quantitative observations will be indicated by frequencies and percentages. Chi-Square test with Yates correction will be used to analyze the categorical variables, shown with cross tabulation. Student t-test will be used for continuous variables. P values <0.05 will be considered as statistically significant.

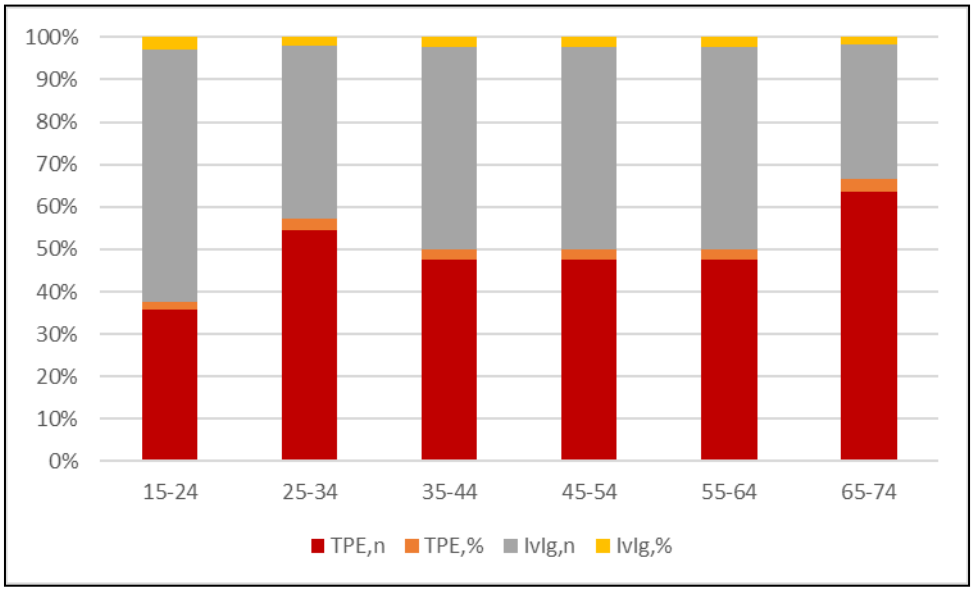

Figure 2: Age distribution of the study patients (n=40)

Table 1: Distribution of the study patients by improvement (%) (n=40)

Parameter	Improvement (%) (TPE cycle)		Ivlg	
	n	%	n	%
▪ Grade 1- only a trace or flicker of muscle contraction is seen or felt	7	35.0	7	35.0
▪ Grade 2- muscle movement is possible with gravity eliminated	4	20.0	4	20.0
▪ Grade 3- muscle movement is possible against gravity	4	20.0	4	20.0
▪ Grade 4- muscle strength is reduced, but movement against resistance is possible	4	20.0	4	20.0
▪ Grade 5-Normal strength	1	5.0	1	5.0

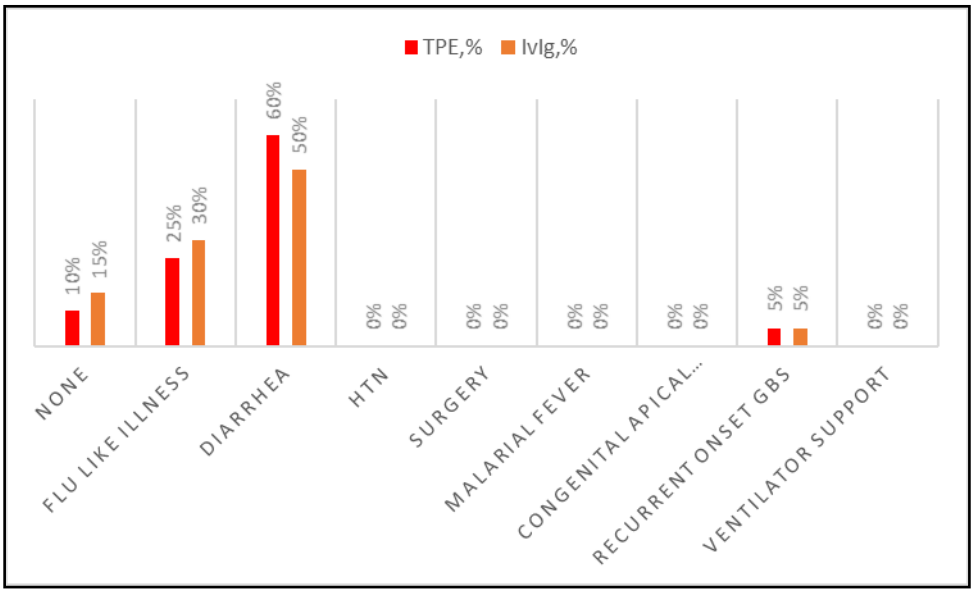

Figure 3: Antecedent event of the study patients

Table 2: Clinical outcome of the patient

Day	Plasma exchange cycle	Plasma volume exchanged (PV)	Power lower limb (B/L)	Power upper limb(B/L)	DTR	Sensory loss	GBS disability score
1	1st	1.3 PV	2/5	3/5	Absent	No	5
2	2nd	1.3 PV	2/5	3/5	Absent	No	5
3	3rd	1.3 PV	2/5	3/5	Absent	No	5
4	4th	1.3 PV	3/5	4/5	Absent	No	5
5	5th	1.3 PV	4/5	5/5	present	No	4
10	-	-	5/5	5/5	present	No	4
20	-	-	Able to stand and walk with aid	Do	present	No	3
30	-	-	Do	Do	present	No	2
45	-	-	Do	Do	present	No	0

*source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5613433/[11]

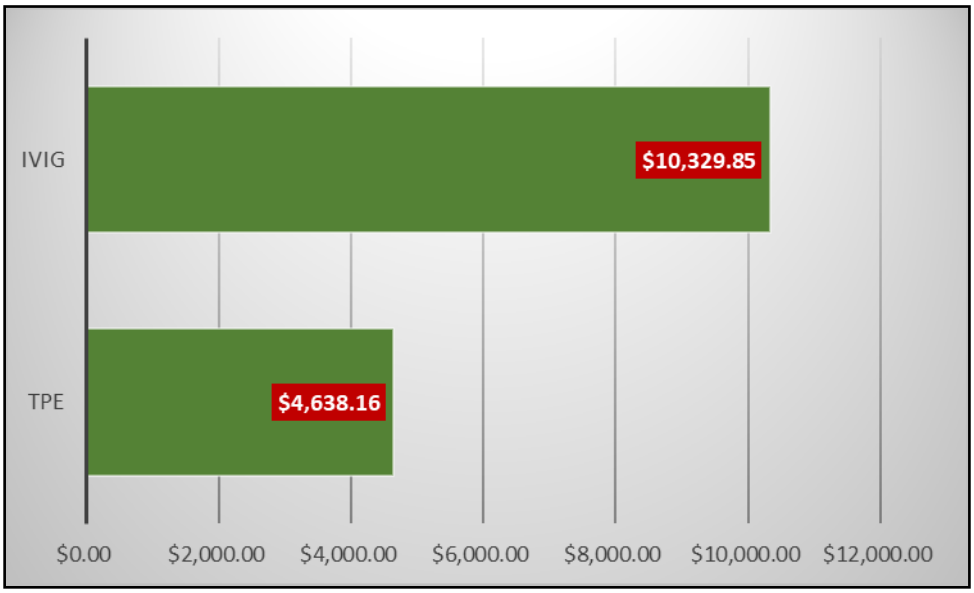

Figure 4: Hospital costs of IVIg therapy and TPE therapy[10]

*source: https://www.ncbi.nlm.nih.gov/pubmed/21575219/

RESULTS

In figure-2 shows age distribution of the study patients (n=40) where it was observed that 4(20.0%) patients belonged to age 25-34 years, 35-44 years and 45-54 years respectively in TPE group and 35-44 years and 45-54 years respectively in IvIg group.

In table-1 shows improvement of the study patients, it was observed that 7(35.0%) patients had Grade 1- only a trace or flicker of muscle contraction is seen or felt in Improvement (%) (TPE cycle) and IvIg group respectively.

In figure-3 antecedent event of the study patients, it was observed that almost two third (60.0%) patients had diarrhea in TPE group and 50.0% in IvIg group. Followed by 25.0% flu like illness in TPE group and 30% in IvIg group.

In table-2 shows clinical outcome of the patient where patient's condition started improving after three cycles of TPE with power in the upper limbs 4/5 and lower limbs 3/5. The patient was also weaned off from ventilator after the 4th TPE. There was progressive improvement in the muscle power in all four limbs within 10 days of admission to our hospital. He started walking with aid in 20 days.

In figure-4 shows hospital costs of IVIg therapy and TPE therapy where direct costs of IVIg therapy are more than twice that of TPE.

DISCUSSION

In this present study, it was showed that 20.0% patients belonged to age 25-34 years, 35-44 years and 45-54 years respectively in TPE group and 35-44 years and 45-54 years respectively in IvIg group. The reported incidence rates for GBS are 1–2 per 100,000 populations and is common in all age groups. One study conducted that nineteen severely paralyzed GBS patients, aged 14–76 years, who were treated between 1998 and 2008, were retrospectively studied.[5] In another study reported that male preponderance with mean age was 40.69 years varied from 10-74 years. In this present study, it was observed that 35.0% patients had Grade 1- only a trace or flicker of muscle contraction is seen or felt in Improvement (%) (TPE cycle) and IvIg group respectively. Grade 2- muscle movement is possible with gravity eliminated was found 20.0% and 20.0% in TPE and IvIg respectively. Grade 3- muscle movement is possible against gravity 20.0% in TPE and 20.0% in IvIg. Grade 4- muscle strength is reduced, but movement against resistance is possible in 20.0% in TPE and 20.0% in IvIg. Grade 5-Normal strength was found 5.0% and 5.0% in TPE and IvIg respectively. Other study demonstrated in their study that at the time of discharge 50 (75.7%) patients showed a marked (grade 3 to 4) improvement in muscle power.[6] Fourteen (21.2%) patients showed mild improvement in (grade 3) muscle power and 2 (3.0%) patients showed no improvement (grade 1 to 2). Duration of ventilation, disability and induces full muscle strength recovery.[7]

TPE helps in non-selective removal of immunoglobulins, complement, and cytokines, thereby altering the pathogenesis of GBS. At the time of discharge 75.7% patients showed clinical improvement in their muscle strength and 99.0% patients scored higher grades of functional outcomes. Other study reported that a short illness accompanied by fever was the most common preceding event followed by diarrhea and upper respiratory tract infection; 62.1% patients gave a history of preceding illness before the onset of symptoms of GBS; 24.2% had flu like illness along with fever as a preceding factor 13.6% patients had diarrhea, 4.5% patients were severely hypertensive, 4.5% patients were having a recurrent onset of the symptoms of GBS and 2 3.0% patients had undergone prior surgery.[6]

History of malarial fever, congenital atypical atrophy and prior respiratory complication was documented in one patient each. Progressive muscle weakness in all four limbs and numbness followed by pain and general discomfort were the most common initial symptoms found in 74.2% patients followed by para paresis in 25.7% patients.

Out of the 66 patients included in the study, 12.1% patients had dysphagia along with quadriparesis, 12.1% patients had respiratory distress, 3.0% patient had dysarthria, and 3.0% patient had change in voice as associated complaining symptom and sign. Although plantar reflex was absent or difficult to elicit in all the patients, 2 of the patients presented with mild sensory impairments and mild paresthesia. 60.6% patients presented with dysautonomia, most common manifestations being cardiac dysfunction such as waxing and waning sinus tachycardia, sinus bradycardia, paroxysmal hypertension and hypotension. Another study reported that most of the patients preceding onset of GBS, the commonest being flu like symptoms followed by gastroenteritis and have also been reported in other studies.[8,9]

Another study said that the direct cost of five IVIg infusion sessions totaling 2.0 grams per kilogram (g/kg) body weight was $10,329.85 compared to a series of five TPE procedures, which had direct costs of $4,638.16.[10]

LIMITATIONS

The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not be reflect the exact picture of the country.

RECOMMENDATIONS

- Further studies can be undertaken by including large number of patients.
- Standard application of TPE is recommended as changing of 200-250 ml plasma per kilogram body weight over in 7-14 days (in each session 50 ml/kg, total 5 exchanges) and use of replacement fluids.
- The use of TPE is recommended in any patient with CIDP who cannot walk unaided or has a more severe deficit (Class I, Level A), who has compromised respiratory function, whose disease cannot be controlled adequately with two months of corticosteroid therapy with a dosage of 1-1.5 mg/kg every other day.

CONCLUSION

After several analysis and investigation, it can be concluded that TPE appears to be a less expensive and most effective first-line therapy option for treatment of patients with GBS. Further study is needed for better outcome.

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