Efficacy and Cost Effectiveness of Therapeutic Plasma Exchange in patient of Guillain-Barre Syndrome – A Prospective study

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ABSTRACT

Introduction: Guillain-Barre syndrome (GBS) is an acute, frequently severe, fulminant poly-radiculoneuropathy that is autoimmune in nature. Current treatment modalities include therapeutic plasma exchange (TPE) and high dose intravenous Immunoglobulin therapy (I.V Ig), both of which involve a high cost. **Objectives:** To compare the cost effectiveness of plasma exchange over other modalities and to evaluate the clinical benefits of plasma exchange GBS patients. **Discussion:** In the present study, 100 patients (56 males and 44 females) admitted to the Civil Hospital, Ahmedabad from September 2010 to August 2012 with clinical findings of GBS and/or GBS variants were evaluated. Plasma was exchanged using a Baxter-CS 3000 continuous flow cell separator using double lumen femoral catheter, until a plasma discard of 50ml/kg had been achieved. Cost of treatment with plasma exchange for each patient was compared with other available modalities. Incidence of GBS was found to be more in 11-30 years age group. Male to female ratio was 1.27: 1. Most of the patients underwent 3 cycles of exchange. The result of plasma exchange in terms of improvement in clinical condition of patient was Excellent i.e. more than 85% in 82 patients. No complication was seen in 62 patients and minor complications were observed in 21 patients. The cost of plasma exchange and immunoglobulin treatment were came out to be approximately Rs 30,000/- and Rs. 1, 74,000/- in each patient respectively. **Conclusion:** Plasma exchange proved to be a better and less costly in the treatment of GBS patient if performed in the first two weeks of onset.

Key words: Guillain-Barre syndrome (GBS), Therapeutic Plasma Exchange (TPE), Intravenous Immunoglobulin (IV Ig)

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Introduction

Guillain-Barre syndrome (GBS) is an acute, frequently severe, and fulminant polyradiculoneuropathy that is autoimmune in nature. It occurs in about 3500 cases per year in the United States and Canada.Since the virtual elimination of poliomyelitis,GBS has become the leading cause of acute flaccid paralysis in western countries.[1] Males are at 1.5 fold higher risk for GBS than females, and in western countries adults are more frequently affected than children.[2]

Approximately two thirds of cases are preceded by an acute, influenza-like illness from which the affected individuals have recovered by the time the neuropathy has become symptomatic. Infection with Campylobacter jejuni, Cytomegalovirus, Epstein Barr virus and Mycoplasma pneumonia, or prior vaccination, has shown to have a significant epidemiologic association with Guillain-Barre syndrome.[3]Circulating autoantibodies are responsible for acute attack. Treatment with medications that suppress the activities of the immune system and/or reduce inflammation of the tissues has been the most common approach to autoimmune disease for more than 30 years but all the medications used to treat autoimmune disease have serious side effects when taken in high doses for months or years.[4] Various treatment options have been investigated based on the immune mediated and inflammatory nature of the disease. The randomised controlled trial published in 1978, indicated no beneficial effect of corticosteroids.[5] Current treatment modalities include therapeutic plasma exchange and high dose Immunoglobulin therapy. A lot of cost is involved in both these modalities. As the patients coming to the clinics of Civil Hospital belong to poor socioeconomic class, all the cost is borne by the hospital and patients are treated free of cost.

Objectives:

- To compare the cost effectiveness of plasma exchange over other modalities
- To evaluate the clinical benefits of plasma exchange in the patients of GBS.

Results and Discussion:

In the present study, 100 patients with the age range of 11 to 68 years admitted to civil hospital, Ahmedabad from September 2010 to August 2012, who were referred to us for performing TPE, were evaluated. All patients had clinical findings of GBS and/or GBS variants.

During the study period, the patients who fulfilled clinical findings and recognised diagnostic criteria (Cerebrospinal fluid (CSF) protein levels and Electromyography studies) for GBS and were treated with TPE, were selected, after obtaining informed consent from the relative of the patients. Total 303 procedures were performed for 100 patients. A minimum of 1 and maximum of 5 cycles of plasma exchange were performed depending upon the clinical outcome in the patient. The clinical outcome was assessed on the basis of improvement in motor performance (increase in power grade, increase in reflexes) and overall clinical condition. For motor performance Patients were assessed before starting treatment and after completion of each cycle of TPE.

Plasma was exchanged using Baxter C S 3000 continuous flow cell separator using double lumen femoral Catheter, until a plasma discard of 50ml/kg had been achieved. Calcium gluconate infusion (10 ml of calcium gluconate in 1 litter NS) was given during the procedure to prevent citrate toxicity. ACD: whole Blood ratio used was 1:10, Blood flow rate was kept between 30-50 ml/min. depending on the weight and calculated Blood volume of the patient. Depending on the amount of plasma exchange, the duration of procedure varies from 2-2.5 hrs. We were able to achieve the desired plasma exchange in more than 90% of procedures.

Usually 3-5 exchanges were done over a period of 7-12 days, depending upon the clinical condition and further improvement in the patient. The extracorporeal volume in CS-3000 is around 400 ml, which limits its use in paediatric patient or the patient with less body mass index. The separated plasma was replaced with saline (crystalloids) initially and with fresh frozen plasma later on during the procedure.

GBS is the main cause of acute polyneuropathy and it is a frequent cause of neuropathy encountered in practice.[6] The incidence remains almost uniform below the age of 40, ranging from 1.3-1.9 per 100000 annually. Most surveys show a slight peak in late adolescence and young adulthood, coinciding with an increased risk of infections with Cytomegalovirus and Campylobacter Jejuni and a second peak in the elderly.[7,8,9]In our study also the incidence is slightly higher between 11 -30 years age group (Table 1).

Table 1: Age group wise distribution among GBS (Guillain-Barre syndrome**) patients**

Age group (in years)	No. of Patients
11-20	29
21-30	30
31-40	20
41-50	08
51-60	08
61-70	03
71-80	02
Total	100

In most of the studies males are affected more than females which are similar to the present study. Male-Female ratio is 1.25:1. (Male-56,Female-44). Different cases are reported between 8 month and 81 years old. [10, 11, 12]The syndrome often begins with symmetric weakness of feet. [11]In a few days, ascending quick progression of weakness develops total motor paralysis and death may occur due to respiratory insufficiency. In 30% of patients quadriplegia occurs.[6,11,13,14] Vital capacity can decrease below 1 litre and due to respiratory deficiency mechanical ventilator can be required. Autonomic involvement may be seen such as fluctuations in blood pressure, cardiac arrhythmia, urinary retention and ileus. Death develops as a result of pneumonia and hypotension (3-10%) [15,16]Contrary to clinical features mentioned above, several variants of GBS are recognized such as Miller Fisher syndrome, Acute Motor Axonal Neuropathy (AMAN), Acute Motor Sensory Axonal Neuropathy (AMSAN), pharyngeal-brachial and pure sensory variant.[6,10,13,14]In our study we have selected100 patients of acute demyelinated polyneuropathy and 2 of them were of Miller Fisher syndrome.

While GBS remains largely a clinical diagnosis certain tests may be helpful. Diagnosis is established by clinical findings, electro diagnosis and

laboratory studies such as CSF examinations.[16]In about 90% of the patients, CSF pressure is normal and contains only a few lymphocytes or none. The increase of CSF protein is related with diffuse inflammation of nerve roots. In all our patients, protein elevation was found. Electro diagnostic studies usually demonstrate conduction block caused by myelin loss; however unexcitable motor nerves may be found in the axonal forms.[17] Patients were assessed on a disability scale (0=healthy; 1= minor symptoms; 2= able to walk 5m without support; 3= able to walk 5m with support 4=confined to bed or wheelchair; 5=requiring assisted ventilation; 6= dead)[18]

Various treatment modalities have been investigated based on the immune-mediated and inflammatory nature of the disease. Intravenous immunoglobulin (IVIg)has two primary medical uses. First, it is given to supplement patient's immune system with GBS and increase their defence. Second, it can be given to suppress the immune system.[19]The mechanism by which IVIg works in GBS is unclear. IVIg has minimal side effects including headache, local skin reaction at the infusion site, and flu like symptoms. Aseptic meningitis, thromboembolic events such as pulmonary embolism due to increasing viscosity of blood, are seen rarely.[20]

Plasma exchange removes antibodies and other potentially injurious factors from the blood stream. It involves connecting the patient's blood circulation to a machine which exchanges the plasma for a substitute solution, usually albumin. TPE is quite useful in rapidly progressive form of GBS.[10,11,15]In patients in whom TPE was performed in the second week of onset, decrease in period of hospitalization, requirement of ventilation and period of starting mobilization was observed.[14,21,22]In our study the procedure was started within two week of onset of disease in most of the patients. TPE may be a superior treatment option as compared to IVIg in patients with GBS and Electromyography (EMG) findings of axonal involvement.[23]

The recommendations are to use two plasma-exchange treatments for mild GBS and four or five for severe GBS, starting as soon as possible on a schedule of alternating days. In our study, 1 to5 cycles were done as per severity of disease and clinical condition of the patient. Most of the patients (n=57) underwent 3 cycles. .(Table-2 & Figure-2) Several other studies also confirm the results of our

study.[10,21,24]Maximum clinical improvement is seen after 2 cycles and further improvement after 3 cycle. Not all patients have been recommended 5 cycles due to femoral catheter related complication and also citrate toxicity which is frequently seen when the PE cycle is more than 3. Only one cycle was done in 2 patients who did not show any signs of improvement which were diagnosed to be Miller Fisher Syndrome on further workup.

Table 2 Distribution of TPE Cycles

No of patients	No of cycles
07	1
10	2
57	3
23	4
03	5

Table 3 Improvement after TPE

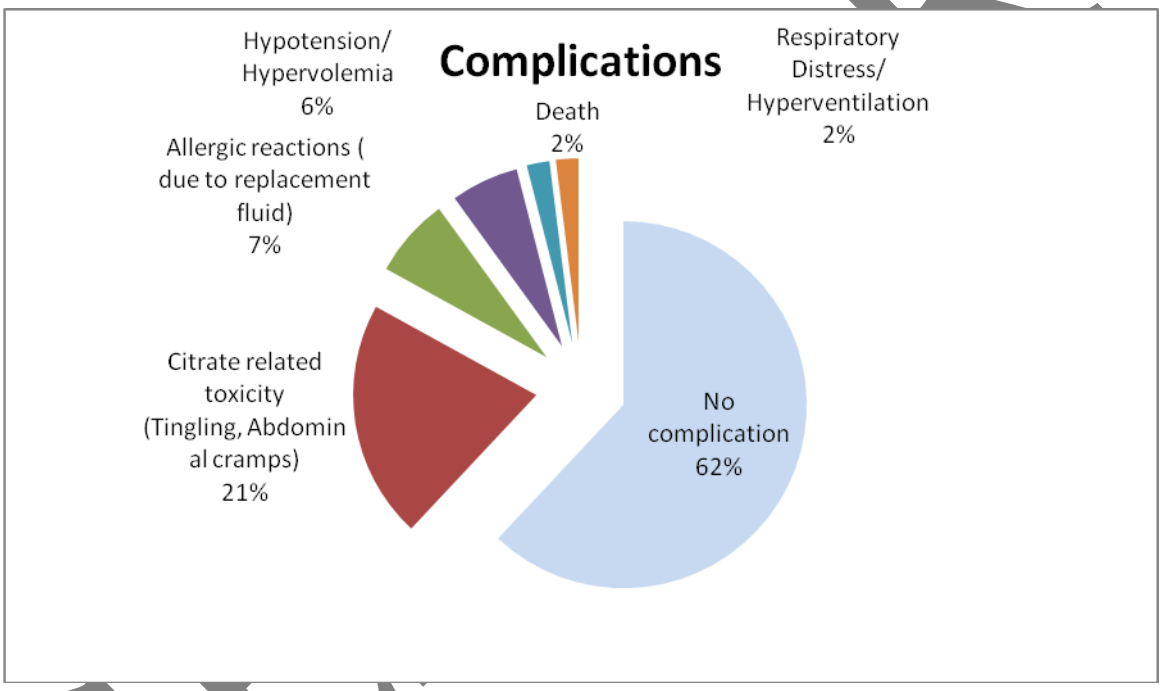
No of Patients	Improvement in %
82	>85%
10	>70%
4	>55%
2	>40%
2	No improvement

TPE- Therapeutic Plasma Exchange

As seen from observations, maximum improvement was observed in 82 patients after the procedure, suggesting that TPE is very effective treatment in GBS patients (Table 3). The response was not good in few patients may be because most of them were of older age group coinciding with the previous studies that age has been shown to have a strong prognostic significance. The patients in the North American trial who were randomised after day 7 were 30 years of age, did not need artificial respiration, received plasma exchange and had Compound Muscle Action Potential (CMAPs) above 20% of normal and were all independently ambulant at 6 month. In contrast if patients were 60 years of age or more and had all the other negative factors, the proportion of patients independently ambulant at 6 month was only 19%[25].Similar results were obtained in a study in the UK.[26]With appropriate care, the prognosis is good, though it is usually better in younger than older individuals. Overall complete recovery is in 85% of patients. The mortality rate is 3-4%.[27] The results coincide with our study showing excellent improvement in >85% patients and mortality rate of 2%. 2 young patients did not show any signs of improvement which later on turned to be Miller Fisher Syndrome.

During the study period, majority of patients (n=62) did not suffer from any complication.(Figure-1) The commonest complications seen during TPE in our study were minor complications like due to citrate toxicity (tingling sensation, cramps) in about 21 patients and allergic or febrile reactions due to the replacement material in 7 patients. Moderate complications like hypotension, hypovolemia and major complication like respiratory distress, catheter blockage, acute pulmonary oedema or circulatory collapse were seen in few patients.

Figure 1 Complications of TPE



TPE- Therapeutic Plasma Exchange

However fatal complications have occurred with an incidence of about 3 in 10,000 procedure like severe anaphylactic reactions to plasma manifesting as acute pulmonary oedema or circulatory collapse and systemic complication related to indwelling venous lines, such as bleeding or septicaemia have been implicated .[18,28,29] Such complication was seen in 1 patient in our study which was due to catheter induced embolism leading to Deep Vein Thrombosis and finally to pulmonary embolism and death of the patient .

Rare complication of TPE includes severe anaphylactic reaction seen during the transfusion of Fresh Frozen Plasma (FFP) as replacement fluid. The risk may be

reduced by using 5% human albumin solution as the replacement fluid and whenever possible, by inserting new, superficial venous catheter for each procedure. Various replacement fluids like crystalloids, albumin, plasma and cryoprecipitate reduced plasma can be used.[30]Though albumin is more preferable than FFP as replacement fluid, in our setup FFP was used because of low socioeconomic status of our patient and we didn't observe any major complication by it. In our study we have compared the cost of each procedure, to that of the other treatment modality –Immunoglobulin. For eg. If we consider cost ofTPE and IVIg in 60 kg GBS patient, one cycle of TPE cost 10,000 Rs. (Including the cost of PE Kit and replacement fluid) Total costs for 3-5 cycles: 30-50,000 Rs. Dose of IVIg for 60 kg of GBS patient is 120 gm for 2 days. So the total cost is Rs1.74 lakh. The cost of IVIg is significantly higher than TPE. It may still increase if the weight of patient is more. (Table-5)

Table -5: Cost Comparison of TPE and IVIg

Cost of TPE (Rs)	Cost of IVIg (Rs)
Per cycle-10,000	Per dose – 87,000 in 60 kg person
Total cost for 3 cycle-30,000	Total cost of 2 dose in 60 kg person- 1,74,000
If 5 cycles required maximum cost will be -50,000	If person is more than 60 kg the cost will increase according to weight.

TPE- Therapeutic Plasma Exchange IVIg- Intravenous Immunoglobulin

During our 2 years study period of 100 patients of GBS, it was observed that plasma exchange was a better option, especially in Government set up, where most of patients were not able to afford expensive modality of treatment such as IVIg and immunosuppressive drugs.

TPE was found to be more cost effective than IVIg as the treatment modality in GBS taking into account the shortening of time interval in Intensive care unit and Hospital. The financial advantage to the patient is of returning to work earlier and lesser hospital payments. The non-financial advantages to the patient include less time on the ventilator, in the intensive care unit, in hospital and able to fulfil their usual role in society.

Conclusion:

TPE proves to be better and cost effective modality in the treatment of GBS patient if performed in the first two weeks, especially in developing countries like India where not many people can afford

expensive treatment modalities, and where Medical Insurance is not common as in developed countries.

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