A Retrospective Study on Patients with Guillain-Barré Syndrome Treated with Therapeutic Plasma Exchange and Other Treatment Options – A Centre’s Experience

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Abstract
Therapeutic plasma exchange (TPE) has been shown to hasten recovery in Guillain-Barré syndrome (GBS). In this study, the objective was to show the outcome of disability grade in a retrospective analysis of data of clinical experience of TPE using the COBE Spectra Apheresis system and other treatment options in selected patients from a series of 56 patients with GBS at a single treatment centre in Turkey. Ten patients had the acute motor axonal neuropathy (AMAN) subtype; 46 had the acute inflammatory demyelinating polyneuropathy (AIDP) subtype of GBS. Three hundred and eighteen TPE procedures were performed taking 2 to 3 hours: in 6.3 % of them a peripheral catheter was used; in 93.7 % of them a central catheter was used. Replacement fluids were fresh frozen plasma (FFP), lactated Ringer’s solution or 3 % hydroxyethyl starch (HES). Among the patients, 12 (21.4 %) who had severe disease course received additional treatment to TPE – this was intravenous immunoglobulin (IVIG) in 11 patients. One patient was treated with steroids after rheumatology consultation due to another autoimmune disease. After 2 weeks, the mean GBS disability scores had significantly decreased from 3.75±0.48 to 2.44±0.96 (p=0.0001) and mean Medical Research Council (MRC) muscle strength scores significantly increased from 2.07±0.89 to 3.54±0.88 (p=0.0001). No difference in efficacy was observed between AMAN and AIDP subtypes. Adverse events occurred in 20 procedures (6.3 %) of TPE and were mostly transient hypocalcaemia and allergic reactions that did not necessitate treatment discontinuation. Difficulty in venous access was observed in 3.14 % of procedures. TPE using the COBE Spectra Apheresis system provides effective treatment of GBS with an acceptable safety profile using various replacement fluids and is an essential part of disease management. Although the benefit is controversial, other treatment options may be applied as an additional therapy in selected patients.

Keywords
Guillain-Barré syndrome, therapeutic plasma exchange, apheresis, disability score, muscle strength, safety profile, single-centre experience

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Guillain-Barré syndrome (GBS) is a rare but acute neuropathy occurring in 1.1–1.8/100,000 of the population (in Europe and North America). GBS manifests as limb weakness, areflexia and sensory loss proceeding to neuromuscular paralysis involving facial, bulbar and respiratory function. Symptoms reach a maximum severity in 2–4 weeks. The neuropathy frequently causes severe and lasting disability, especially difficulty walking and can necessitate ventilator support: 3–13 % of patients die and 20 % are still unable to walk after 6 months. GBS is more frequent with increasing age (0.62/100,000 in 0–9 year olds rising to 2.66/100,000 in 80–89 year olds) and there is a small predominance of male gender. GBS has two subtypes: 1. acute inflammatory demyelinating polyradiculoneuropathy (AIDP) (sensory motor symptoms resulting from demyelinating changes) and 2. acute motor axonal neuropathy (AMAN) (motor symptoms from axonal damage). The aetiology of GBS is not fully understood but it is believed to be a result of autoimmunity – in most cases triggered by infection with pathogens stimulating anti-ganglioside antibodies such as Campylobacter jejuni (diarrhoea), Mycoplasma pneumonia, Haemophilus influenza, cytomegalovirus, Epstein Barr virus and influenza.
Successful treatments for GBS are intravenous immunoglobulin G (IVIG) and therapeutic plasma exchange (TPE) – the latter reduces the autoantibody load by removing IgG, alters the Th1–Th2 ratio, removes cytokines and lessens the severity of symptoms. The full mechanism of action of these treatments, however, is not fully understood.12 TPE has been shown in multiple studies to hasten recovery in GBS. While studies have shown the efficacy of TPE and IVIg to be broadly similar in GBS, IVIg treatment can increase the risk of thrombotic events. Furthermore, treatment with IVIg after TPE does not appear to improve outcomes.13,14 However, in patients with severe disease course, we do not have many choices and in some medical centres both of the treatments have been applied in this group of patients, consecutively.13 This article reports on the application of centrifugal TPE using the COBE Spectra Apheresis system in the treatment of a series of 60 patients with GBS and other treatment options together in selected patients at a medical centre in Turkey, and provides valuable experience in the management of this disease in a wide range of patients.

**Methods**

**Study Design and Patients**

The study retrospectively analysed data from a series of patients with GBS who were treated with TPE at Baskent University Hospital, Adana, Turkey between April 2004 and November 2011. The medical records were analysed for the patient’s demographic data (age, sex), indication for TPE, results of the treatment and complications of the procedures.

**Plasma Exchange Procedure**

TPE in each case was performed using COBE Spectra (COBE Spectra V. 7.0, Terumo BCT, US). This equipment is an established mobile therapeutic apheresis system that uses centrifugal technology and performs customisable procedures for a variety of different patients and applications on one platform.15 TPE was performed every other day for most of the patients and one plasma volume was exchanged during each procedure. The total blood volume was calculated according to body weight (70–75 ml/kg), and the calculation of the plasma volume was based on haematocrit values.16 TPE was performed using either a peripheral or central catheter. Replacement fluids were fresh frozen plasma (FFP), 3 % hydroxyethyl starch (HES), lactated Ringer’s solution (RL), substitute fluid (SF) and mixtures of these.

**Data Collection**

TPE procedures were repeated five to seven times taking into consideration the severity of the disease including disability and muscle strength. Endpoints were: GBS disability score, which ranges from 0 (normal) to 6 (dead). Poor outcomes have been regarded as disability scores ≥3 at 6 months and fairly good outcomes as disability scores ≤2 at 6 months. Medical Research Council (MRC) muscle strength scores are the sum of scores of six muscles from the upper and lower limbs on both sides, scores range from 6 (normal) to 0 (quadrilegic).17 The severity of abnormal findings in neurological examination just after the procedure and 2 weeks later was compared with that before the beginning of the treatment. Adverse events recorded during and after treatment were collected. Data were extracted from previously authorised and validated hospital data management systems (Hospital Data Management System; Version 1.5; Datasel Information Systems, Ankara, Turkey; Nucleus Hospital Information Management System, Version v9.2.40; Monad Software and Counselling, Ankara, Turkey). The accuracy of the data was checked by a group attending for supervision of data records.

IVIg was given 0.4 g/kg daily, on 5 consecutive days in selected patients.

**Results**

The population comprised 60 patients with GBS. Four patients were excluded: one declined consent after only one procedure and three due to uncertainty of the GBS diagnosis. Data for patient characteristics showed a well-distributed cohort with similar mean and median values, there were no skewed data and standard deviations were within acceptable limits (see Table 1). Ten patients had the AMAN subtype (16.7 %); 46 had the AIDP subtype (76.7 %).

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**Table 1: Characteristics of 56 patients with Guillain-Barré Syndrome**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>TBV (ml)</th>
<th>Plasma Volume (ml)</th>
<th>Hb (g/dl)</th>
<th>HTC (%)</th>
<th>WBC* (×10^9/L)</th>
<th>PLT* (×10^9/L)</th>
<th>Number of Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>16</td>
<td>3,250</td>
<td>1,800</td>
<td>8.3</td>
<td>24.2</td>
<td>77.1</td>
<td>1</td>
</tr>
<tr>
<td>Maximum</td>
<td>78</td>
<td>7,080</td>
<td>4,522</td>
<td>17.2</td>
<td>52.0</td>
<td>14.8</td>
<td>525.0</td>
</tr>
<tr>
<td>Median</td>
<td>52</td>
<td>4,752</td>
<td>2,918</td>
<td>13.9</td>
<td>41.0</td>
<td>9.9</td>
<td>253.0</td>
</tr>
<tr>
<td>Average</td>
<td>50.7</td>
<td>4,818.1</td>
<td>2,964.8</td>
<td>13.5</td>
<td>40.0</td>
<td>9.3</td>
<td>255.7</td>
</tr>
<tr>
<td>SD</td>
<td>15.9</td>
<td>836.2</td>
<td>613.4</td>
<td>2.1</td>
<td>6.3</td>
<td>3.0</td>
<td>84.6</td>
</tr>
</tbody>
</table>

* At first procedure. Hb = haemoglobin; HTC = haematocrit; PLT = platelet; SD = standard deviation; TBV = total blood volume; WBC = white blood cell.

**Table 2: Therapeutic Plasma Exchange Volumes Used in a Series of 56 Patients with Guillain-Barré Syndrome**

<table>
<thead>
<tr>
<th>Replacement Fluid Used</th>
<th>Volume Exchanged</th>
<th>Procedure Time (Minutes)</th>
<th>Volume Processed</th>
<th>ACD-A (ml)</th>
<th>Inlet Flow</th>
<th>Plasma Volumes Exchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>886</td>
<td>1,004</td>
<td>46</td>
<td>2,304</td>
<td>137</td>
<td>40</td>
</tr>
<tr>
<td>Maximum</td>
<td>4,036</td>
<td>4,450</td>
<td>217</td>
<td>12,574</td>
<td>985</td>
<td>70</td>
</tr>
<tr>
<td>Median</td>
<td>2,713</td>
<td>3,095</td>
<td>125</td>
<td>6,531</td>
<td>369</td>
<td>55</td>
</tr>
<tr>
<td>Average</td>
<td>2,778.7</td>
<td>3,129.6</td>
<td>126.0</td>
<td>6,666.9</td>
<td>378.7</td>
<td>53.3</td>
</tr>
<tr>
<td>SD</td>
<td>461.4</td>
<td>491.5</td>
<td>23.1</td>
<td>1,493.4</td>
<td>91.0</td>
<td>5.5</td>
</tr>
</tbody>
</table>

ACD-A = anticoagulant citrate dextrose solution; solution A; SD = standard deviation.
A total of 318 TPE procedures were performed. Of these, 20 (6.3%) used a peripheral catheter, the remainder (93.7%) used a central catheter. Each apheresis procedure took about 2–3 hours. The mean number of TPE procedures was 5.3 (range from 5 to 7; median: 5). The volumes replaced, however, were fairly consistent (see Table 2). Albumin could not be used as the replacement fluid due to government insurance reimbursement regulations. Instead, FFP, RL, SF or HES solutions were used. The replacement fluid consisted of 50% FFP and 50% RL, SF or HES. There were no additional complications associated with the replacement fluids during and after the procedures.

After 2 weeks, TPE treatment significantly improved both GBS disability and MRC muscle strength scores compared with scores prior to treatment (see Figure 1). The mean GBS disability score before TPE was 3.75±0.48 (range: 3–5) decreasing to 2.44±0.96 after TPE, range: 1 to 6 (p<0.0001). The MRC muscle strength score before TPE was 2.07±0.89 (range: 0–3) and this increased to 3.54±0.88 after TPE, range: 0–5 (p<0.0001). No difference in these parameters was observed between ADP and AMAN subtypes. Among the patients, 12 (21.4%) who had severe disease course received additional treatment to TPE; this was IVIG in 11 patients. One patient was treated with steroids after rheumatology consultation due to another autoimmune disease. Long term data for six (54.5%) patients showed improvements and maintenance of disability and MRC muscle strength scores in three (27.2%) patients, but worsening in disability scores in two (18.1%) patients who received IVIG after TPE treatments.

Adverse events only occurred in 20 of the 318 procedures (6.3%) and were mostly hypocalcaemia and allergic reactions (see Table 3) that required oral calcium supplementation and anti-allergic drugs. None of these events justified discontinuing the session. Difficulties with venous access were recorded 10 times (3.14%). No technical problems related to cell separators were noted.

Four patients died but these were not related to the treatment. Of these, two patients had respiratory muscle involvement who did not improve after the procedure. One patient with GBS died after a single procedure from multi-organ failure (this patient was already excluded). One patient died in another centre 2 months after the procedure due to myocardial failure.

Discussion
The retrospective analysis of 7.5 years of data from one treatment centre showed that in a series of 56 patients with GBS, treatment with TPE provided significant improvements in both GBS disability scores and MRC muscle strength scores. Partial long-term data show that in a subgroup of the patients the improvements following treatment were mostly sustained. TPE was well tolerated; adverse events associated with the treatment were limited in terms of incidence and severity. The most frequent adverse event was mild hypocalcaemia – this is frequently reported in TPE especially when citrate is used as an anticoagulant and is believed to readily bind calcium ions in the blood. This event, however, only occurred after 12 procedures so did not appear to constitute a serious safety concern. The use of FFP is associated with an increased risk of infection but this did not appear to be the case in this set of patients. Previous studies showed no efficacy differences between FFP and albumin-replacement fluids. Earlier work also showed that the combination of the GBS disability score and the MRC scores assessed at 1 or 2 weeks are good predictors of outcomes at 6 months and this justifies the use of these two parameters as endpoints in this study. The results reported here are generally in agreement with those of previous studies that compared TPE with supportive treatment in GBS. A meta-analysis of six trials totalling 649 patients showed that in some of the trials, TPE treatment significantly decreased the time to regain walking ability (30 versus 44 days) and decreased the proportion with walking disability after four weeks (risk ratio [RR]: 1.60). In addition, TPE also reduced the need for ventilation support compared with controls (RR: 0.53). Patients receiving TPE, however, were more likely to relapse than controls. Nevertheless, after 1 year, patients treated with TPE were significantly more likely to have regained original muscle strength (RR: 1.24) and less likely to have motor sequelae (RR: 0.65). The treatment used in this study is in line with various guidelines that state treatment with TPE or IVIG within 2–4 weeks of GBS onset hastens recovery in GBS. Guidelines from the American Society for Apheresis categorise TPE treatment in GBS as Grade 1A (Category I) i.e. a strong recommendation with high-quality evidence. Corticosteroids are often used in GBS treatments but some guidelines state that these drugs do not improve outcomes and are not recommended. These guidelines also emphasise that TPE treatment must commence within 2–4 weeks of onset to be effective and prevent long-term sequelae. The American Academy of Neurology Guidelines (2011) assigned class one evidence for the use TPE in GBS.

It is generally accepted that the mechanism of action of TPE in GBS is primarily the removal of auto antibodies and other protein factors and the replacement of plasma components (when FFP is used as the replacement fluid). However, the treatment may also promote
lymphocyte proliferation and sensitisation and alter B- and T-cell numbers and activation. The exact mode of action of TPE in GBS therefore needs further investigation and may assist the development of improved approaches to managing the disease.

Currently TPE and IVIG are the only effective treatments for GBS and studies show that despite treatment with TPE and IVIG, 20% of patients with GBS remain unable to walk and 5% die.1,2,3 New, possibly less-aggressive, treatments therefore are an urgent medical need. The results of this study show that TPE using the COBE Spectra Apheresis system provides effective treatment of GBS that has an acceptable safety profile with varied replacement fluid formulations and is an essential component of disease management particularly in patients for whom IVIG administration is inappropriate.

IVIG and PE appear to have equivalent efficacy in treatment of GBS. The optimal dose and schedule of both PE and IVG for this condition is unclear. Prior studies have shown that for the moderate to severe group, four sessions were beneficial.24 In our study, TPE procedures were repeated five to seven times taking into consideration the severity of the disease including disability and muscle strength. Regarding the number of IVIG treatments, in one study all the patients were given 0.4 g/kg daily, on five consecutive days, similar to our patients.25 Another study indicated that six IVIG sessions may be more beneficial than three in more severe patients.26

There has not been so many studies in which both of the therapies have been applied. To apply both of the treatments would cost so much and there have not been many results about the application of the two treatments in the same patient. However, in patients with severe disease course, we do not have many choices, so we may use our other chance at least in this kind of patients. The best treatment option for patients with GBS that continue to deteriorate despite initial therapy with IVIG or PE alone is unclear. The therapeutic difficulty is because of the variability of the course of the GBS in individual patients. To apply IVIG after PE seems more reasonable because the apheresis may remove some of the immunoglobulins administered to the patient. So we applied IVIG after PE in necessary patients. In a study by Ozcko-Walker et al., a small group of patients were applied PE after IVIG who had severe impairment after completion of IVIG, and did not show significant improvement after PE.3 In another study, the median time to recover unaided walking was found less than in patients who received PE alone, however, this difference was not significant.25 Hughes et al. suggests more research particularly to show the results of the combination therapy especially for those patients who do not respond.25 The patients with severe course may not improve with any kind of treatment, but we cannot learn this or we cannot have evidence-based results if we do not apply and see the results. There has not been any exact information on the interval between TPE and IVIG in literature as there have been only a few studies that applied both of the treatments.

The patients who have severe disease course are generally conspicuous from the beginning or some patients go on deteriorating despite treatment with TPE. In these kinds of patients IVIG can be given just after the TPE treatment finished. Or, occasionally, some patients deteriorate over a period of time, for example, after a week of TPE treatment. Then, in these patients IVIG could be given at that time. So, it can be suggested that the decision could be made for the interval between TPE and IVIG, individually.

An increased number of studies from different medical centres will strengthen the results and provide more accurate suggestions for patients. Such studies would be important for the literature in terms of a different medical centre’s results and applying both PE and IVIG in some of the patients with their reasons.