

A treatment experience of intravenous immunoglobulin and therapeutic plasma exchange in a neurology clinic for 5 years

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SUMMARY

The aim of this study was to monitor intravenous immunoglobulin (IVIG) therapy and therapeutic plasma exchange (TPE) in three different neuroimmunological diseases.

A total of 50 patients with Guillain-Barré syndrome (GBS), 22 with chronic inflammatory demyelinating polyneuropathy (CIDP), and 13 myasthenia gravis (MG) were retrospectively reviewed in terms of treatment efficacy.

No significant difference was found between Hughes and Medical Research Council (MRC) sum scale at the time of admission and 3 months after admission in patients with GBS who received IVIG and TPE treatment. Further, no significant difference was observed between the MRC sum scale and the overall disability status scale at the time of admission and 3 months after admission in patients with CIDP who received IVIG and TPE treatment. Although the Osserman scores of the patients with MG receiving TPE treatment were higher than those of the patients with MG receiving IVIG treatment, the Osserman scores after 3 months of admission did not differ significantly.

This study concluded that IVIG treatment and TPE did not differ in terms of treatment efficacy in the case of common neuroimmunological diseases.

Key words: Intravenous immunoglobulin, neuroimmunological disease, therapeutic plasma exchange

INTRODUCTION

Intravenous immunoglobulin (IVIG) is a biological agent obtained from the blood fraction of 2000–16,000 patients. The immunomodulatory mechanisms of IVIG are varied, such as inhibiting Membrane Attack Complex (MAC) formation and complement activation, decreasing antibody production, neutralizing pathogenic cytokines, modulating macrophage-mediated phagocytosis, and modulating T-cell functions and antigen recognition. Therapeutic plasma exchange (TPE) is a blood separation technique that removes immunologically active molecules such as antibodies, immunoglobulins, complements, and cytokines (1). Both IVIG and TPE have been found to be effective in the treatment and stabilization of many neurological diseases where autoimmunity is effective (1, 2-6).

Guillain-Barré syndrome (GBS) is an autoimmune polyneuropathy that may result in acute inflammatory demyelinating polyradiculopathy or acute axonal motor or motor and sensorial axonal neuropathy in pathological substrates (7). Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronic, acquired immunodeficient neurological condition that affects the peripheral nervous system (8). Myasthenia gravis (MG) is an autoimmune neuromuscular junction disease caused by autoantibodies against frequently acetylcholine receptors in various proteins in the motor endplate (9). GBS, CIDP, and MG are effective treatments for both disease remission and treatment in both IVIG and TPE.

The aim of this study was to compare the efficacy of IVIG and TPE for maintenance therapy in patients with GBS, CIDP, and MG in the clinic.

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MATERIALS AND METHODS

The medical records of 50 patients with GBS, 22 patients with CIDP, and 13 patients with MG, who were treated at the neurology clinic, were retrospectively reviewed between January 2012 and May 2016. Patient diagnoses were established with current clinical status and electrodiagnostic tests. Clinical and demographic characteristics, neurological examinations, treatments, and complications were recorded from the patient files. Patients in each of the three disease groups were excluded from the study when patients receiving IVIG or TPE treatment had complications related to treatment and received both treatment modalities. The disability status was determined by examining the Hughes and the Medical Research Council (MRC) sum scale at the time of admission and 3 months after the admission for patients with GBS. The disability status was determined by examining the MRC sum and overall disability status scale (ODSS) at the time of admission and 3 months after the admission for patients with CIDP. The Osserman score was calculated for patients with MG at the time of admission and 3 months after the admission. The Hughes scale assesses the functional ability of the patient, with a strong emphasis on mobility. The Hughes scale of patients included in this study ranged from 0 (no symptoms or signs) to 5 (requiring artificial ventilation for at least part of the day) (10). The MRC sum score is a summation of the MRC grades (range, 0–5) given in full numbers of the following muscle pairs: upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsal flexors. The MRC sum score ranges from 0 (“total paralysis”) to 60 (“normal strength”). Good validity and interobserver reliability for this scale have been demonstrated (10). The ODSS is composed of a recently published arm and leg disability scale (11,12). Ossermann classification was used for staging, with patients’ clinical stage distribution as follows: grade I (ocular involvement); grade IIa (mild generalized ocular myasthenia); grade IIb (moderate generalized myasthenia involving bulbar musculature); grade III (acute fulminant form); and grade IV (severe late myasthenia) (13). The IVIG-treated group was administered with IVIG at a dose of 0.4 g/kg for five consecutive days. In the group receiving TPE treatment, all TPE procedures were performed using the central venous catheter. The device used in all procedures was COBE Spectra (Lakewood, CO, USA), which works with continuous flow. Total blood and plasma volumes were calculated using standard formulations.

Albumin–saline, ISOHES, Ringer lactate, and fresh–frozen plasma were selected as replacement fluids according to the clinical and laboratory parameters of the patients. TPE was administered for five sessions every other day.

Statistical analysis

Gender, number of patient groups and treatment methods, and number and percentage distributions of the individuals included in the study were recorded. The Kruskal–Wallis nonparametric test was used to analyze whether the ages of the individuals in the study were significantly different between groups of patients. The chi-square test was used to determine any difference between the gender groups of patients, and the result of Pearson chi-square was noted. The Mann–Whitney U nonparametric test was used to analyze whether Hughes scale at the time of admission for the patients with GBS included in the study, Hughes scale 3 months after the admission, MRC sum scale at the time of admission, and MRC sum scale 3 months after the admission differed among the IVIG and TPE treatment groups. Also, the Mann–Whitney U nonparametric test was used to analyze whether the MRC sum scale of the patients in the study, the MRC sum scale of the admission, the MRC sum scale after 3 months of admission, the ODSS at the time of application, and the ODSS after 3 months of application differed among the IVIG and TPE treatment groups. The Mann–Whitney U nonparametric test was used to analyze whether Osserman’s score at the time of admission of the patients with MG included in the study and Osserman scores after 3 months of admission differed among the IVIG and TPE treatment groups. For statistical analysis and calculations, IBM SPSS Statistics 21.0 (IBM Corp. released 2012. IBM SPSS Statistics for Windows, version 21.0, NY, USA) and MS–Excel 2007 programs for some calculations were used. The statistical significance level was accepted as $P < 0.05$.

RESULTS

Of the 85 participants in the study, 53 were men and 32 were women. Further, 58.8% ($n = 50$) had GBS, 25.9% ($n = 22$) had CIDP, and 15.3% ($n = 13$) had MG. Also, 73 individuals received IVIG treatment and 12 received TPE treatment (Table 1).

The Hughes scale average of the 45 patients in the GBS group who received IVIG treatment and those who received TPE treatment was 2.60 ± 1.69 and 2.80 ± 2.04 , respectively. Further, the Hughes

TABLE 1: Demographic characteristics of patients.

Demographic characteristics	n (%)
Gender	
Men	53 (62.4)
Women	32 (37.6)
Patient group	
Guillain-Barré syndrome	50 (58.8)
Cronic inflamatuar demyelinizan polinoropatya	22 (25.9)
Myastenia gravis	13 (15.3)
Treatment methods	
IVIG	73 (85.9)
TPE	12 (14.1)

IVIG: Intravenous immunoglobulin; TPE: Therapeutic plasma exchange.

scale average of patients with GBS who received IVIG treatment was 1.28 ± 1.74 , whereas the Hughes score average of the patients who received TPE treatment was 1.00 ± 1.41 after 3 months of admission. The MRC sum scale average of patients with GBS who received IVIG treatment at the time of admission was 47.17 ± 10.63 , whereas the MRC sum scale was at the time of admission of patients who received TPE treatment was 49.20 ± 7.82 . The MRC sum scale average of patients with GBS who received IVIG treatment was 52.68 ± 10.83 after 3 months of admission, whereas the MRC sum scale average of patients who received TPE treatment was 55.20 ± 6.57 after 3 months of admission. No

statistically significant differences were found between Hughes scale and MRC sum scale at the time of admission and 3 months after the admission for patients with GBS ($P=0.717, 0.783, 0.806$, and 0.798 , respectively) (Table 2).

The mean of the MRC sum scale of patients with CIDP who received IVIG treatment at the time of admission and 3 months after the admission was 51.30 ± 7.08 and 54.10 ± 7.12 , respectively. The ODSS average of patients with CIDP who received IVIG treatment at the time of the admission and 3 months after the admission was 3.30 ± 2.90 and 2.20 ± 2.30 , respectively. The mean MRC sum scale of patients with TPE at the time of admission and 3 months after the admission was 52.50 ± 6.36 and 58.50 ± 2.12 , respectively. The ODSS average of patients with TPE at the time of admission and 3 months after the admission was 2.50 ± 0.70 and 1.00 ± 1.41 , respectively. No statistically significant differences were found in the MRC sum scale and ODSS average at the time of admission and 3 months after the admission ($P=0.815, 0.539, 0.861$, and 0.518 , respectively) (Table 3).

The Osseman score average of patients with MG who received IVIG treatment at the time of admission and 3 months after the admission was 2.25 ± 1.03 and 1.62 ± 0.51 , respectively. The Osseman score average of patients who received TPE treatment was 3.60 ± 0.54 at the time of referral and 3.40 ± 0.54 3 months after the admission. The Osseman scores of the treatment group showed statistically significant differences ($P=0.028$). The Osseman scores of patients

TABLE 2: Hughes scale and MRC sum scale at the time of admission and 3 months after admission of patients with GBS who received IVIG and TPE treatments.

Variables	Treatment group		Test statistic	
	IVIG (n = 45) Mean ± SS Median (IQR)	TPE (n = 5) Mean ± SS Median (IQR)	Z	P
Hughes scale at the time of admission	2.60 ± 1.69 3.00 (3.00)	2.80 ± 2.04 2.00 (4.00)	0.362	0.717
Hughes scale after 3 months of admission	1.28 ± 1.74 0.00 (3.00)	1.00 ± 1.41 0.00 (2.50)	0.275	0.783
MRC sum scale at the time of admission	47.17 ± 10.63 48.00 (16.00)	49.20 ± 7.82 54.00 (12.00)	0.245	0.806
MRC sum scale after 3 months of admission	52.68 ± 10.83 60.00 (13.50)	55.20 ± 6.57 60.00 (12.00)	0.256	0.798

MRC: Medical Research Council.

TABLE 3: MRC sum scale and ODSS at the time of admission and 3 months after admission of patients with CIDP who received IVIG and TPE treatments.

Variables	Treatment group		Test statistic	
	IVIG (n = 20) Mean ± SS Median (IQR)	TPE (n = 2) Mean ± SS Median (IQR)	Z	P
MRC sum scale at the time of admission	51.30 ± 7.08 54.00 (12.00)	52.50 ± 6.36 52.50 (-)	0.233	0.815
MRC sum scale after 3 months of admission	54.10 ± 7.12 57.00 (12.00)	58.50 ± 2.12 58.50 (-)	0.615	0.539
ODSS at the time of admission	3.30 ± 2.90 2.00 (4.75)	2.50 ± 0.70 2.50 (-)	0.175	0.861
ODSS after 3 months of admission	2.20 ± 2.30 2.00 (3.75)	1.00 ± 1.41 1.00 (-)	0.646	0.518

MRC, Medical Research Council; ODSS, overall disability status scale.

who received TPE treatment were higher than the scores of those who received IVIG treatment. No statistically significant difference was observed between the Osseman scores 3 months after the treatment ($P=0.447$) (Table 4).

DISCUSSION

This study investigated the efficacy of IVIG and TPE treatments in neuroimmunological diseases, which are common in the clinic. No difference was found in the treatment efficiency for patients with GBS and CIDP in the case of disability at the time of referral and after 3 months of referral. However, in patients with MG, the Osseman score was significantly higher in the TPE group than in the IVIG group. Besides, no significant difference was found in Osseman scores after 3 months for patients with MG. This suggested a trend for the use of TPE when starting immunomodulatory therapy in

patients with MG whose clinical findings are heavier, but this did not affect clinical outcomes in the long term.

Both IVIG and TPE are agents used to provide immunomodulation in many neurological diseases. Randomized clinical trials have shown that both treatment modalities have similar efficacy, benefit duration, and safety profile (14-18).

GBS is a disease that results in damage to neuronal tissues caused by cross-reactivity of antibodies against a microbial agent (19). IVIG and TPE treatment in GBS was started in 1988 and 1985, respectively (20, 21). In 1992, both treatments displayed similar efficacy in a study conducted on the IVIG and TPE treatment groups (6). No difference was observed between IVIG and TPE in patients with GBS who were treated within 2 weeks of the Cochrane Library's review publication in 2012 (7). In a study on GBS, IVIG alone, TPE

TABLE 4: Osseman scores at the time of admission and 3 months after admission of patients with MG who received IVIG and TPE treatments.

Variables	Treatment group		Test statistic	
	IVIG (n = 8) Mean ± SS Median (IQR)	TPE (n = 5) Mean ± SS Median (IQR)	Z	P
Osseman score at the time of admission	2.25 ± 1.03 2.00 (1.75)	3.60 ± 0.54 4.00 (1.00)	2.199	0.028
Osseman score after three months of admission	1.62 ± 0.51 2.00 (1.00)	1.40 ± 0.54 1.00 (1.00)	0.761	0.447

alone, and TPE followed by IVIG showed no superiority compared with each other (22-25). In the present study, no difference was found between IVIG and TPE treatments in patients with GBS. In a study conducted on pediatric patients with GBS, a more significant improvement in bulbar and respiratory functions was noted in the IVIG treatment group compared with the TPE treatment group (26-28). These different outcomes might be due to the heterogeneous nature of the disease and differences in the pathogenesis.

CIDP is a chronic, acquired, immunologically mediated disease of the peripheral nervous system.⁸ Previous studies have shown that IVIG and TPE have a similar effect on CIDP in the short term (29-31). Both treatment modalities showed similar efficacy in this study.

MG is an autoimmune neuromuscular disease caused by antibodies against postsynaptic nicotinic acetylcholine receptors.¹ Although both treatment modalities were effective treatment methods for stabilizing the disease in patients with MG, TPE in patients with myasthenic crisis and IVIG in patients with progressive MG patients were found to be more effective in the short term (1, 32-34). TPE treatment is preferred in patients with MG when the clinical control is weak or in clinical situations where rapid clinical correction is intended, such as a myasthenic crisis or preoperative preparation (1, 33). This was supported by the finding that the Osserman score was high in patients with MG who received TPE in this study.

Since TPE is a more difficult treatment method, IVIG is the first choice in treating neuroimmunological diseases in most centers. In this study, 85.9% of the patients received IVIG treatment and 14.1% received TPE treatment. Also, both treatment methods were associated with some difficulties. IVIG is an expensive, time-consuming treatment method, with some challenges at times. On the contrary, TPE is an invasive method that requires a central venous catheter according to the method of administration and should be applied by well-trained personnel at private centers (29).

Complications that may develop due to IVIG include headache, nausea, fever, aseptic meningitis, and heart and kidney failure. IVIG is contraindicated in patients with immunoglobulin A deficiency and those who have previously developed an allergic reaction to any immunoglobulin. TPE is a reliable treatment method, which is often well tolerated but has some complications. TPE due to

catheter application may cause pneumothorax, catheter infection, and venous thrombosis. Complications such as hypotension and vasovagal symptoms due to saline infusion may also be seen. Further, some relative contraindications such as coagulopathy and thrombocytopenia are noted in TPE (29).

This study had some limitations: (1) it was retrospectively designed and had a relatively small sample size; and (2) the disability scales used were insufficient to detect some significant clinical situations, although they were simple, valid, and reliable. Still, this study provided information about the management of neuroimmunological diseases. Prospective studies evaluating the efficacy and necessity of IVIG and TPE in patients with mild GBS, the efficacy of IVIG and TPE in providing long-term remission in CIDP, and the efficacy of IVIG and TPE in patients with MG before surgery are needed.

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