Therapeutic Effect of Plasma Exchange in Steroid Refractory Inflammatory Demyelination of Central Nervous System: Outcome from a Tertiary Centre in Malaysia

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Abstract

Objective: To evaluate the efficacy of plasma exchange (PLEX) in steroid refractory inflammatory demyelination diseases (IDD) of Central nervous system (CNS).

Methods: Retrospective review of patients presented with steroid refractory IDD from 2006 to 2016 that underwent PLEX. Clinical data on neurological assessment, time to treatment initiation, visual acuity (VA) and Expanded Disability Status Scale (EDSS) were gathered from the medical records. The primary outcome was improvement at 3 months after PLEX. Statistical analysis was done using the SPSS version 21.

Results: Forty-three plasma exchanges were performed involving 27 patients (NMOSD= 22, RRMS= 4, ITM= 1). The mean age of patient was 43.60 ± 15.18, and the mean EDSS was 7.98 ± 1.07 at presentation. The anti-AQP4 antibody was detected in 81.5%. Treatment success was observed in 21/43 (48.8%) of patients with a significant improvement of 2.13 EDSS point post PLEX. A lower baseline EDSS score ≤ 6 showed a trend toward good outcome (p= 0.07). AQP4 status had no influence on treatment outcome. Male gender, preserved reflexes, use of DMT and shorter time to PLEX initiation, were not associated with treatment outcome.

Conclusion: PLEX is an effective treatment for steroid refractory IDD, regardless of the AQP4 antibody status. A lower baseline EDSS might be associated with a better treatment outcome. PLEX should be considered irrespective of the symptom duration.

Keywords: Plasma exchange (PLEX); Steroid refractory IDD; AQP4

Abbreviations: PLEX: Plasma Exchange; AQP4: Aquaporin 4; DMT: Disease Modifying Therapy; EDSS: Expanded Disability Status Scale; ON: Optic Nerve; TM: Transverse Myelitis; VB: Vertebral Bodies; RRMS: Relapsing Remitting Multiple Sclerosis; NMOSD: Neuromyelitis Optica Spectrum Disorder; ITM: Idiopathic Transverse Myelitis.

Introduction

Plasma exchange (PLEX) is a treatment process in which 1.1 to 1.5 plasma volumes are being filtered by continuous-flow centrifugation using either 5% human albumin or fresh frozen plasma as replacement solutions. The latest Evidence-based guideline update on the role of PLEX in neurologic disorders by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) has provided a Level A evidence on the effectiveness of this treatment modality in severe Gullain-Barre Syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP), and a Class III evidence in the treatment of severe exacerbation of myasthenia gravis (MG) [1]. Its role as a treatment modality for steroid refractory, immune-mediated demyelinating diseases of the central nervous system (CNS) has been established since the 1980’s, particularly in acute relapses of Multiple sclerosis (MS) and Neuromyelitis optica spectrum disorders (NMOSD) [1,2]. In general, a total of 5 to 7 exchanges are performed when there is no significant neurological improvement observed 2 weeks after completion of high dose intravenous corticosteroid. The interval is shortened if deficits continue to worsen after steroids administration. The beneficial effect of PLEX has been reported in 40 to 90% of patients with steroid unresponsive demyelinating diseases of the CNS [3]. In 2011, the American Academy of Neurology has considered PLEX as probably effective for treatment escalation therapy in steroid refractory relapses of MS and other fulminant demyelinating diseases of the CNS (class IB and II C evidence respectively) [1]. The good predictors of response include male gender, preserved reflexes and shorter time to PLEX initiation [4].

This is a retrospective study to evaluate the effect of therapeutic PLEX in patients presented to our centre with steroid refractory, immune-mediated demyelinating diseases of the CNS. Factors associated with treatment outcome were identified and discussed.

Methodology

We retrospectively identified a total of 27 patients admitted to our Neurology unit in University Malaya Medical Centre, Kuala Lumpur, who underwent 43 courses of PLEX (consisting of 5 cycles of of PLEX on alternate days) for the treatment of steroid refractory inflammatory demyelinating diseases (IDD) of the CNS using the Blood Bank Apheresis records from the year 2006 until 2016. Two patients were excluded due to unavailability of medical records during the period of plasma exchange. PLEX was conducted using either Spectra Optia (Terumo BCT, Lakewood, CO, USA) or Amicus (Fressening Krabi, Bad Hamburg, Germany) machines, using acid citrate dextrose formula A (ACDA) as the anti-coagulant in a 10:1 and 12:1 ratio respectively. Between 1.0 and 1.5 plasma volumes were treated in each session every other day. Each patient underwent a total of five cycles of PLEX, using 5% human albumin as the replacement solution.

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on neurological assessment, time to treatment initiation, visual acuity (VA) and Expanded Disability Status Scale (EDSS) were gathered from the medical records. The primary outcome was improvement at 3 months after PLEX. No or mild improvement is defined as no gain of neurological function or definite improvement in neurologic status without impact on function. Moderate improvement is defined as definite improvement in function, and marked improvement is defined as major improvement in function. Treatment success is defined as a decrease of ≥ 1 point in the EDSS score for patients with EDSS ≤ 7.5 or back to baseline with EDSS ≥ 8.0, or improvement of more than 2 lines in the VA chart for patients with optic neuritis (ON). Hence, treatment success includes patients with moderate and marked improvement after PLEX. Statistical analysis was done using the SPSS version 21. Descriptive data was expressed as total numbers and percentages; elsewhere, parametric data was analyzed using the Student’s t-test and nonparametric data using the Chi square test. Values of p<0.05 were considered statistically significant.

Results

Demographics

In total, 43 courses of PLEX treatments were performed for steroid refractory IDD, involving 27 patients. All patients received an initial course of high dose intravenous corticosteroid (a total of 5 gram) prior to the initiation of 5 cycles of PLEX. There was a female predominance, with a female to male ratio of 8:1. Anti-AQP4 antibody was detected in 81.5% of patients. Chinese was the predominant racial group affected (23/27, 85.2%), followed by the Malay (4/27, 14.8%). The mean age at relapse was 43.60 (± 15.18) years with a high mean EDSS of 7.98 (± 1.07). Twenty-two (51.2%) patients were on Disease modifying treatment (DMT) that consisted of Azathioprine (4), β-Interferon (3), Mitoxantrone (10), Mycophenalate mofetil (4) and Rituximab (1) at the time of relapse (Table 1).

Clinical parameters

Twenty six patients (92.3%) had a relapsing course. The most common presentation was transverse myelitis (26/43, 60.5%), followed by optic neuritis (14/43, 32.6%) and cortical syndrome (3/43, 7.0%). Only 15/26 cases of transverse myelitis (TM) had accompanying MRI of the spine, and all were associated with lesion extending more than 3 vertebral bodies. The diagnosis at the last follow up was NMOSD (n= 22, 81.5%), RRMS (n= 4, 14.8%), and Idiopathic transverse myelitis (ITM) (n= 1, 3.7%). Moderate to marked improvement, also defined as treatment success, was observed in 21/43 (48.8%) of patients (Table 1). The median interval from symptom onset to initiation of PLEX in the treatment success group was 14 days (± SD 15.91, range 2-66), and 18 days (± SD 16.17, range 2–71) in the treatment failure group. A significant improvement of 2.13 EDSS point was observed in the treatment success group (p=0.002) as opposed to 0.13 point in the treatment failure group (p=0.03) at 3 months follow up post PLEX (Table 2). There was no significant difference in the outcome after PLEX based on age at relapse, gender, disease duration, anti-AQP4 on neurological assessment, time to treatment initiation, visual acuity (VA) and Expanded Disability Status Scale (EDSS) were gathered from the medical records. The primary outcome was improvement at 3 months after PLEX. No or mild improvement is defined as no gain of neurological function or definite improvement in neurologic status without impact on function. Moderate improvement is defined as definite improvement in function, and marked improvement is defined as major improvement in function. Treatment success is defined as a decrease of ≥ 1 point in the EDSS score for patients with EDSS ≤ 7.5 or back to baseline with EDSS ≥ 8.0, or improvement of more than 2 lines in the VA chart for patients with optic neuritis (ON). Hence, treatment success includes patients with moderate and marked improvement after PLEX. Statistical analysis was done using the SPSS version 21. Descriptive data was expressed as total numbers and percentages; elsewhere, parametric data was analyzed using the Student’s t-test and nonparametric data using the Chi square test. Values of p<0.05 were considered statistically significant.

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| Total PLEX, n | 43 |
|---------------|----|
| Gender, n (%) |    |
| F             | 24 (88.89%) |
| M             | 3 (11.11%)  |
| Ethnic, n (%) |    |
| Malay         | 4 (14.81%)  |
| Chinese       | 23 (85.19%) |
| AQP4 status, n (%) |    |
| Positive      | 22 (81.48%) |
| Negative      | 5 (18.52%)  |
| DMT, n (%)    |    |
| Yes           | 22 (51.16%) |
| No            | 21 (48.84%) |
| Age at relapse|    |
| Years ± SD    | 43.60 ± 15.18 |
| Range         | 16 - 78     |
| Disease duration at relapse |    |
| Years ± SD    | 6.81 ± 6.04  |
| Range         | 1 - 37     |
| EDSS at relapse|    |
| Years ± SD    | 7.98 ± 1.07  |
| Range         | 4.5 - 9.5  |
| Clinical course|    |
| Monophasic    | 1 (3.7%)    |
| Relapsing     | 26 (92.3%)  |
| ON (n = 14)   |    |
| Unilateral    | 11 (78.57%) |
| Bilateral     | 3 (21.43%) |
| TM (n = 26)   |    |
| Imaging NA    | 11 |
| >3 VB         | 15 (100.00%) |
| Cortical (n = 3) |    |
| Extensive     | 2 (66.67%)  |
| < 2 cm        | 1 (33.33%)  |
| Diagnosis |    |
| RRMS          | 4 (14.81%)  |
| NMOSD (+ve)   | 21 (77.78%) |
| NMOSD (-ve)   | 1 (3.70%)   |
| ITM           | 1 (3.70%)   |
| Response to PLEX |    |
| No/ mild response | 22/43 (51.16%) |
| Moderate response | 6/43 (13.95%) |
| Good response | 15/43 (34.88%) |

PLEX= Plasma Exchange, AQP4= Aquaporin 4, DMT= Disease modifying therapy, EDSS= Expanded Disability Status Scale, ON= Optic nerve, NA= Not available, TM= Transverse myelitis, VB= Vertebral bodies, RRMS= Relapsing remitting multiple sclerosis, NMOSD= Neuromyelitis optica spectrum disorder, ITM= Idiopathic transverse myelitis.

Table 1: Demographic data.
antibody status and interval to initiation of PLEX. Clinical factors such as preserved reflexes, proprioception and up-going plantar response also did not have any significant impact on the outcome. Baseline EDSS at relapse showed a positive trend toward a good outcome. However, it was not statistically significant (p = 0.07). In contrast, a good baseline VA, defined as VA of 6/6 to 6/9, did not follow a similar trend of outcome. Concomitant DMT at the time of relapse also did not have significant effect on treatment outcome (Table 3). Three patients experienced adverse events associated with PLEX. One patient developed local bleeding due to iatrogenic arterial puncture, 1 patient developed indwelling line-related disseminated sepsis, and 1 patient developed transient hypotension that resolved with concurrent administration of intravenous normal saline infusion. Otherwise, PLEX was well tolerated in other patients.

Discussion

The potential efficacy of PLEX for the treatment of IDD of the CNS was based on multiple case series, and a limited number of randomized control studies. The foundation for its therapeutic effects on immune mediated disorders is attributed to the immediate removal from blood of antibody, cytokines and complements deposition, pulsed induction of antibody redistribution and subsequent immunomodulation. The landmark randomized, sham control study by Weinshenker et al. in 1999 showed a moderate to good improvement in terms of power scores (p=0.027) and EDSS (p=0.032) after PLEX in 42% of patients with steroid refractory MS and other IDD of the CNS. Keegan et al. further support the mechanism of action of PLEX, in which only patients with pattern II MS pathology, characterized by antibody/complement-associated demyelination, responded to PLEX for fulminant demyelinating attack [5]. As Neuromyelitis optica (NMO) lesions are strongly associated with IgG, IgM and complement-dependant toxicity against the astrocytes, which is typical for the pattern II in the Lassmann classification, therapeutic PLEX is associated with favorable outcome [6].

The result of this study was derived from a total of 43 courses of PLEX treatments involving 27 patients over a period of 10 years, with the diagnosis of NMOSD (81.5%), RRMS (14.8%) and ITM (3.7%) who presented with acute relapse, unresponsive to high dose intravenous corticosteroid. Functional improvement, measured by the changes in EDSS and VA post PLEX, was observed in 48.8% of patients. Even though the percentage was lower as compared to recent series by Aungsumart et al. and Ehler et al., it was still consistent with the beneficial treatment effect of PLEX in steroid refractory IDD [3,7]. The patient population was dominated with sero-positive NMOSD, which contributed to a high mean EDSS of 7.98 ± 1.07 at relapse. This can be explained by the high concentration of AQP4 receptors especially in the spinal cord grey matter and optic nerves, resulting in a more extensive inflammation and neurological deficits. PLEX was associated with significant improvement in EDSS in the treatment success group, with a mean EDSS improvement of 2.13 points as compared to 0.13 point in the treatment failure group (p=0.002).

Time to PLEX initiation was considered as essential predictor of good outcome. Llufriu et al. in her series of 41 patients with acute attack of CNS demyelination revealed a reduction in success rates from 83% to 43% when PLEX was delayed from within 15 days to 2 months respectively [8]. The concept of “Time is Cord and Eyes” was further explored by Bonnan et al. who postulated that the hypothetical correlation of lesion stages in spinal attacks in NMO and PLEX effects could be divided into 3 stages. Stage 1 is the hyper-acute process of antibody driven immune-mediated inflammation characterized by edema. Stage 2 ensues a few days after the acute event and consists of the excitotoxic effect of glutamate on oligodendrocytes that resulted in demyelination and axonal loss. PLEX is postulated to be most effective in stage 1 and incomplete in stage 2. Weeks later, Stage 3 is characterized by prominent astrocytic, oligodendrocytic and axonal loss, associated with necrosis, where PLEX is assumed to be ineffective [6]. Despite the important role of antibody/complement mediated inflammation in acute attacks of IDD, treatment outcome was independent of the AQP4 status, suggestive of a complex and heterogeneous immune-pathological mechanism [6,7,9]. Interestingly, a shorter time to PLEX initiation did not show any significant effect on the treatment outcome in our study. This was echoed by Ehlers et al. in her series of 90 patients with Clinically isolated syndrome (CIS) and MS, and Aungsumart in her series of 21 patients with NMOSD [7]. Hence, even though a short time to initiation of PLEX should be prioritized to interrupt the inflammatory process, favorable outcome might still be achievable irrespective of the duration of symptom onset. In contrast to the study

| Treatment success group (n= 21) | mean (± SD) | p value |
|--------------------------------|-------------|---------|
| EDSS before PE                 | 6.96 (± 1.86) | 0.001*  |
| EDSS upon discharge            | 5.79 (± 1.96) | 0.002*  |
| EDSS upon discharge            | 5.79 (± 1.96) | 0.002*  |
| EDSS at 3 month f/u            | 4.83 (± 2.15) | 0.000*  |
| EDSS before PE                 | 6.96 (± 1.86) | 0.000*  |
| EDSS at 3 month f/u            | 4.83 (± 2.15) | 0.000*  |

| Treatment failure group (n= 22) | mean (± SD) | p value |
|--------------------------------|-------------|---------|
| EDSS before PE                 | 7.04 (± 2.12) | 0.021*  |
| EDSS upon discharge            | 6.93 (± 2.07) | 0.329   |
| EDSS upon discharge            | 6.93 (± 2.07) | 0.329   |
| EDSS at 3 month f/u            | 6.91 (± 2.05) | 0.030*  |
| EDSS before PE                 | 7.04 (± 2.12) | 0.030*  |
| EDSS at 3 month f/u            | 6.91 (± 2.05) | 0.030*  |

| Overall EDSS with PE | mean (± SD) | p value |
|----------------------|-------------|---------|
| EDSS before PE       | 7.83 (± 1.32) | 0.000*  |
| EDSS at 3 month f/u  | 6.34 (± 2.20) | 0.000*  |

Table 2: EDSS with PLEX.
by Ehlers et al. involving a cohort of patients with MS spectrum disorder, our study did not show significant association between concurrent use of DMT and PLEX treatment [3]. Nevertheless, our cohort of patients was dominated by NMOSD in which acute attacks were associated with intense antibody-mediated response. Hence, acute attacks were more supportive of failure of DMT.

**Conclusion**

The only factor that showed a trend toward predicting a good outcome after PLEX was a lower baseline EDSS (p=0.07). This was also observed in other studies involving both MS and NMO spectrum disorders [3,6,7]. As 92.3% of our patients showed a relapsing form of illness, the lower EDSS might be a reflection of a preserved neurological reservoir with the ability to promote neuronal repair. On the other hand, a good baseline VA did not follow the same trend of outcome. This might be explained by the intense process of immune-mediated inflammation against a smaller surface area of optic nerves as compared to the cortex and spinal cord, which resulted in a more extensive neuronal damage and poorer neuronal reserve. Worthy of note, the presence of radiographic features such as gadolinium enhancement which represents disruption of blood brain barrier indicative of active disease, and cord atrophy that suggests poor neurological reserve, are important good predictors of outcome [3,7]. Unfortunately, due to the retrospective nature of this study, radiological study was only available in 41.9% of patients with only 12/18 (cortical= 3, spinal cord= 9) of the imaging performed during the acute relapse which showed gadolinium enhancement and edema. Nine patients (75.0%) from this cohort had a favorable outcome after PE [10-12]. In conclusion, PLEX is a safe and effective treatment for steroid refractory IDD, regardless of the AQP4 antibody status. A lower baseline EDSS might reflect a better neuronal reservoir which translated into a better treatment outcome. Even though shorter time to treatment initiation is essential for a better outcome, PLEX should be considered irrespective of the symptom duration as a favorable outcome is still achievable. We acknowledge the limitation of our study, being retrospective and small sample size. Prospective studies with larger sample size that incorporate serial imaging should be encouraged.

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