Therapeutic plasma exchange in CNS inflammatory demyelinating disorders: time is brain and spine?

Key Points
- There is emerging evidence that early TPE in NMOSD relapses results in more favourable outcomes.
- Although the optimal timing is unclear, there is increasing evidence that early TPE within the first two days may offer the greatest degree of recovery in NMOSD relapses.
- Given underlying shared immunological mechanisms between NMOSD and other CNS-IDD, there may be potential benefit of early TPE in this spectrum of disorders. This is a further direction of research.

Abstract
TPE has a role in the management of various immune-mediated neurological disorders including CNS inflammatory demyelinating disorders (CNS-IDD), often as second line treatment following high dose steroids in part due to perceived risk, which inevitably result in delays in accessing TPE.

There has been limited evidence such delays impact long-term outcome, however emerging data suggests that even 10-14 days, typical of when TPE is reserved for steroid-unresponsive patients, may adversely affect outcomes. We review TPE use in CNS-IDD, focusing on emerging data on timing and implications for clinical practice.

The role of TPE – Protocols and Mechanisms of Action
Therapeutic plasma exchange (TPE), an apheresis technique first established in 1952, is a process which removes plasma from the circulatory system. There is offset with physiological fluid replacement, usually human albumin preparations or fresh frozen plasma (FFP). The cellular components of the plasma initially removed are subsequently returned in this part of the cycle. TPE is traditionally performed via central venous catheters but can be performed by peripheral access providing the flow is sufficient.

The purpose of TPE is twofold. It allows the replacement of factors deficient in the plasma of patients.

In addition, TPE allows the removal of abnormal circulating proteins, toxins or antibodies which are implicated in the clinical and pathological manifestations of an underlying disorder. CNS-IDD, which comprises of conditions such as Multiple Sclerosis (MS), Clinically Isolated Syndrome (CIS) and Neuromyelitis Optica Spectrum Disorder (NMOSD) have an immunological basis for their pathophysiology that makes TPE an attractive treatment option.

Given antibodies such as IgG are large molecular weight molecules which have a long half-life of 21 days, TPE is highly efficacious as it allows the rapid removal of relevant pathogenic autoantibodies involved in the underlying disorder.

One plasma volume of TPE removes approximately 65% of intravascular constituents and two plasma volumes about 85%. Due to a potential rebound phenomenon in IgG levels following 1-2 cycles, most centres typically perform more procedures (4-5 cycles) to maintain lower levels of circulating pathogenic antibodies.

Rapid reduction of immunoglobulins by 60-70% of baseline titres following a plasma exchange series has been noted. Recovery of levels for most immunoglobulin subclasses approached baseline levels after six weeks post TPE, in line with previous evidence showing a duration of benefit of TPE of at least four weeks.

There are other mechanisms of action proposed for plasma exchange in addition to the removal of antibodies and replacement of deficient circulating factors. These include a variety of immunomodulatory effects and adaptations including the clearance of immune complexes, cytokines and upregulation of the complement activating system.

Adverse effects of TPE
Previous estimates of TPE complication rates in the literature range from 15-28%, with serious complications from 5-22%.

One study involved 230 exchanges performed in 134 Myasthenia Gravis (MG) patients, with 44% being inpatients. Over 75% of cases were performed with a peripheral venous catheter.

Central venous catheters (CVC) were associated with more total (68% vs 35%) and serious complications (41% vs 4%) compared to peripheral access respectively. However, it should be noted that a significant proportion of TPE via CVC’s (38%) were performed in ICU and the total complication rate is high due to events defined as a complication – these included asymptomatic hypotension requiring a fluid bolus.

In another study of 42 moderate to severe MG patients, 45% had mild reactions not requiring termination of the procedure. These included citrate toxicity and peripheral vascular access issues. 2% had a serious complication where the procedure was abandoned. The majority were treated in the outpatient setting (90%) and via peripheral venous access (83%).

Older patients were more likely to have complications related to TPE. A study comparing TPE between older (>65 years) and younger (<65 years) groups included a total of 4722 treatment sessions for 581 patients. 31.8% of these...
patients were in the older cohort accounting for 1289 sessions, reflecting that TPE is not an uncommon procedure in this age demographic. Indications for TPE were predominantly neurological, haematological and renal related disorders. For patients undergoing TPE for neurological conditions, complications with the TPE procedure were 14% overall: 18.3% in the older cohort, compared to 11.4% in the younger cohort. These included hypotension, coagulopathy, allergies, nausea and flushing. Complications with access placements were 4.2% overall: 7.3% in the older group compared to 2.3% in the younger group. These included infection and access clotting. However, 30 day mortality rates did not differ between the two groups. Similar trends of adverse effects were noted for TPE performed for non-neurological indications.

**Evidence of TPE in CNS-IDD**

The role of TPE in CNS-IDD was initially established by a small randomised, sham-controlled, double-masked study of plasma exchange in MS patients with an acute attack refractory to first line parenteral corticosteroid treatment. The delay to TPE from symptom onset was between three weeks and three months. In addition, a delay of two weeks following administration of first line intravenous corticosteroids was required prior to TPE commencement. Seven cycles on alternate days over 14 days were performed, with crossover to the opposite group for a further seven cycles if the first treatment phase did not result in at least moderate improvement. In the first treatment phase, the responder rate for such improvement was 45.5% (5/11) and 9% (1/11) for the active versus sham groups respectively. Including crossover phases, the responder rate was 42.1% (8/19) and 5.9% (1/17) in active versus sham groups respectively. Including crossover phases, the responder rate was 42.1% (8/19) and 5.9% (1/17) in active versus sham groups respectively. Further studies since then have identified mixed findings. The timing of TPE onset from symptom relapse as a predictor of response has had mixed findings. In one study, the highest responder rate was when TPE was commenced before 21 days. This was corroborated by another study where earlier treatment within 16 days since relapse, had a responder rate of 63.3%, which declined progressively to 42.9% when TPE was commenced more than 60 days following symptom onset. This was not however supported by another study, which showed similar responder rates irrespective of commencement before or after 21 days, out to commencement over 60 days. In addition, other series have not found any correlation between response to TPE in relation to onset of relapse however it should be noted that in these studies the delay to TPE from relapse ranged from 1-3 months.

**Emerging evidence for TPE in NMOSD**

Effective treatment is particularly important as it is well recognised that NMOSD is an aggressive relapsing CNS demyelinating disorder. The mean number of episodes of optic neuritis resulting in blindness is less than two and the mean number of spinal cord relapses resulting in paraplegia is three. Most studies utilised TPE as a second line rescue treatment subsequent to unsuccessful first line therapy, which was predominantly corticosteroids, showing a 50-85% response rate. These typically involved 5 sessions of TPE, although ranged from 2-11 cycles, with 1-1.5 plasma volume exchanges. Replacement fluid was either human albumin 5% or normal saline. An alternate daily or daily regimen were generally used in the administration of protocols with no studies offering a direct comparison between these two in terms of efficacy or tolerability. There is a growing body of evidence for better prognostic outcomes of earlier plasma exchange from time of an acute attack. One study showed patients with moderate to marked improvement compared to minimal or none had a median delayed time to TPE of 14 days versus 51 days respectively. In another study, partial and complete responder rates for TPE initiated less than three weeks from symptom onset was 85.2% compared to 14.8% when TPE was delayed after day 7.

Furthermore, another study involving a predominant Afro-Caribbean population with severe NMOSD attacks also supported earlier treatment. The probability of achieving a complete response to TPE when patients were treated at day 0-1 from symptom onset was 50%. This continuously declined with longer delays to TPE, with complete response rates falling to 5% or less after day 20. However, the intention of TPE in this study unlike most others was that it was not designed as second line therapy, but rather as first line therapy; Steroid use concomitantly occurred in 58-81% of cases depending on the site of the lesion, however even when these were excluded, the response rates to TPE showed a similar downward trend with increasing delays to treatment.

Optimal timing of TPE initiation was unable to be determined in this study due to insufficient patient recruitment, with no significant difference when commenced by day 1 or by day 5. However, beyond day 5, there was a significant decrease in the probability of recovery to baseline. This is an important consideration as restricting TPE as second line therapy in NMOSD attacks may result in delays to effective treatment if first line therapy is unsuccessful. Most steroid treatment protocols range between 3-5 days and are only associated with complete response rates of up to 35%, in line with previous studies. Hence there are inherent delays to TPE rescue therapy being considered whilst first line therapies are being administered and then subsequently assessed for response. This is further corroborated by a further study which found that 40% of patients who started apheresis as first line therapy within two days had a complete response to baseline compared with less than 4% of those who commenced apheresis after six days. At least partial response however, was still observed in over 80% of patients who had started apheresis after six days. This further supports the notion of optimal timing being as early as possible following relapse, potentially within the first 48 hours. The role of TPE in mild to moderate attacks is less clear as first line therapy.

**Immunoadsorption as an emerging alternative**

Immunoadsorption (IA) has emerged in the 1990s as an alternative to TPE in the treatment of neurological disorders including CNS-IDD. Although TPE is still the recommended modality. Unlike TPE, IA does not require the exchange of blood solutions. IA is a blood purification technique that allows selective removal of potential pathogenic humoral factors such as immunoglobulins from plasma via a high affinity adsorbent such as tryptophan. There is evidence to support IA having a superior safety profile over TPE however a recent larger study showed similar adverse rates. Reasons may include less allergic reactions as IA does not require replacement blood solutions. It also potentially allows for less plasma volume shifts during exchanges, which may have less haemodynamic implications. Bleeding risk in IA may be reduced as less coagulation factors are adsorbed.

Immunoadsorption may have limited utility in certain neurological conditions, specifically MuSK Ab Myasthenia Gravis. Tryptophan adsorbent ligand has varying affinities for different IgG subclasses: high for IgG3 (eg. anti-ganglioside antibody), moderate affinity for IgG1 (eg. Anti-AQP4 Ab, anti-ACHR Ab) and low for IgG2 and IgG4 (eg. MuSK Ab). In addition, the availability and access to IA may be limited in many centres compared to TPE.

**Use of Immunoadsorption in CNS-IDD**

There is evidence of similar efficacy of IA and TPE in NMOSD and MS flares.

A recent retrospective study used either IA or TPE in 140 patients with steroid-refractory MS or NMOSD patients where it appeared equally safe (3.6% vs 3.9% respectively). In the MS cohort, IA and TPE were equally efficacious, although owing to only one NMOSD patient undergoing IA, the comparison in this cohort was limited. However, a retrospective study in NMOSD patients not only showed equal efficacy in both apheresis modalities but as previously mentioned, also supported higher recovery rates with shorter delays to treatment, notably when either technique was employed as first line therapy.
Discussion
Corticosteroids have been the main first line therapy for CNS-IDD due to ease of access, administration and relative safety profile. Certain conditions within CNS-IDD such as NMO/SD is perhaps less steroid responsive.12 In addition, NMOSD attacks are generally more severe, conferring a poorer prognosis, hence effective and timely treatment is important. TPE has been shown to be effective in CNS-IDD with a favourable adverse effect profile. TPE is well tolerated, with low serious complication rates.
Complication rates vary based on multiple factors including centre experience, definition of complication, but is higher in the older population, central venous catheters and with increasing severity of illness. technical factors related to the TPE machine and procedural aspects may also play a role in reducing adverse rates with greater advances in technology and expertise of administration. Various prognostic factors predicting response to TPE have been described.13,14 Favourable prognostic factors include early initiation to TPE, early response to TPE, ring enhancing lesions, associated oedema, preserved reflexes and male gender.
Early initiation to TPE is an important consideration, given it is a variable that can be controlled to a degree allowing for other issues such as treatment access. There is competing evidence in several CNS-IDD series with regards to greater benefit in those with TPE commencement within 21 days of relapse. There were other CIS and MS relapse trials that had found no relation to timing of TPE and responder rates however the initiation period was 1-3 months following relapse.
There is stronger evidence in NMO/SD that earlier initiation in TPE confers a more favourable outcome. More recently, there is greater evidence that early TPE within two to five days of symptom onset may offer the greatest degree of recovery for patients, declining progressively subsequently, even with delays of only one week.15
For this reason, incorporating TPE earlier, or even as part of first line therapy in NMOSD should be considered, given the overall poorer prognosis associated with such attacks. TPE declines in efficacy with time, as seen when implemented late as rescue therapy in steroid resistant cases. Retrospectively, this may have initially confounded the degree of benefit from what has now emerged as a highly efficacious treatment when used in an appropriate timeframe. Conversely there is also a risk of overestimating the benefit of TPE where institutions offer this mode of therapy routinely as first line in clinical attacks of all severities. Nevertheless, there is mounting evidence to support the timely use of TPE in NMOSD attacks that is becoming difficult to disregard.
How translatable this is to other conditions within the CNS-IDD spectrum is unknown. Many of the CNS-IDD studies involving MS and CIS had TPE commencement 3 weeks after relapse onset, thereby limiting the contribution of these findings with regards to the utility of TPE in the hyperacute period. Given the likelihood of shared underlying immunological mechanisms of different CNS-IDD, TPE may be similarly effective in the first few days of more disabling attacks in conditions outside of NMOSD. This is a further direction for research.
The concept of TPE as first line therapy in NMOSD is gaining traction as cumulative evidence supports this approach.13,14 This would not only have implications on access protocols in TPE capable hospitals but also on outer district hospitals that they serve. Once again, the role which TPE plays in other CNS-IDD as potentially first line or adjunct therapy, that is concurrent therapy to corticosteroids as opposed to rescue therapy, needs to be better defined.
There is upcoming evidence that IA may be used as an alternative to TPE in CNS-IDD given it appears to have similar efficacy. There is conflicting evidence regarding a superior safety profile with IA which needs further clarification.
Conclusions
There is emerging evidence that early TPE in NMOSD relapses results in more favourable outcomes, with greater than half of patients accruing disability with delays in TPE greater than one week post symptom onset. This proportion increases with progressive delays to treatment. Practically, timely access to TPE should be considered in NMOSD relapses, potentially concurrently with IV steroids. In this clinical context it would appear ‘time is brain and spine’. This points to a clear direction for research to provide insight into these unanswered questions. How reproducible this concept is in other CNS inflammatory demyelinating disorders remains unclear, although there is some evidence indicating a similar trend. Once again, the void in this arena provides an impetus for further research.

Acknowledgment

REFERENCES