

Plasma Exchange to Treat Acute Transverse Myelitis

Brian G. Weinshenker, MD, FRCP(C)
Professor of Neurology
Mayo Clinic and Mayo Foundation
Rochester, MN

Plasma exchange is a treatment wherein blood is circulated via an intravenous catheter outside of the body and separated into liquid plasma components and cellular components by continuous centrifugation. The liquid portion of blood is removed and replaced with an artificial plasma, such as albumin or colloidal starch. Plasma exchange is an effective treatment in several immune-mediated diseases affecting the central nervous system and other body systems (e.g., Goodpasture's disease that affects the kidneys). Among the neurological diseases known to benefit from treatment with plasma exchange are acute and chronic forms of inflammatory demyelinating peripheral nerve disease, such as Guillain Barré syndrome. This might suggest that inflammatory demyelinating diseases affecting the central nervous system such as multiple sclerosis and acute transverse myelitis (ATM) might also respond.

ATM is a syndrome, but one that is most commonly caused by inflammatory demyelination in the spinal cord, and is generally believed to be immune-mediated. In its prototypic form, ATM is distinguishable from attacks of myelitis resulting from multiple sclerosis. ATM typically follows viral infection and results in relatively severe, symmetrical involvement of strength, sensation, and bowel and bladder function. Typically, ATM results in longitudinally extensive lesions with significant cord swelling on MRI. Debate continues on the ability of physicians to discriminate between acute transverse myelitis, which is generally conceived to be a monophasic disease without recurrence, and multiple sclerosis, which is considered to be a relapsing and recurrent disease. Some relapsing illnesses, such as neuromyelitis optica, however, result in relapses of prototypic ATM as described above. It is important to emphasize that prototypic ATM is an acute inflammatory demyelinating disease of the central nervous system. The etiology for isolated ATM, MS and neuromyelitis optica is unknown, and it is unclear whether the clinical and radiological distinctions between them are relevant to the mechanisms by which disability is produced. It is possible that similar effector systems of the immune system operate in both conditions. Substantial immunopathological evidence has accumulated pointing to a role for humoral (plasma-mediated) effector mechanisms and complement activation in both MS and neuromyelitis optica. Such evidence includes the presence of activated complement (C9neo) and antibody bound to myelin oligodendrocyte glycoprotein in pathological samples of patients with MS. Activated complement has been demonstrated in pathological material from patients with NMO.

Plasma exchange has been explored since 1980 as a treatment for multiple sclerosis and other inflammatory demyelinating diseases of the central nervous system such as acute disseminated encephalomyelitis. Uncontrolled series have included both patients with progressive forms of MS and patients with acute, severe attacks of demyelinating disease.

The results of plasma exchange in patients with progressive forms of MS remain controversial. More promising, in our opinion, were the results in patients with acute severe attacks of demyelinating disease. Twenty nine patients in twelve case reports, who had suffered acute, severe neurological deficits, experienced a rapid response with sustained improvement shortly after beginning plasma exchange treatment. Often, benefit was observed after the first one or two treatments. However, there is a well-known bias to report positive results. To confirm the promising results of these controlled series, a prospective, randomized study was needed with excellent masking of the treatment from both physician and patient.

Accordingly, we conducted a randomized clinical trial over 4 years in 22 patients with acute, idiopathic inflammatory demyelinating diseases of recent onset, including acute transverse myelitis between 1995 and 1998 at Mayo Clinic. All patients enrolled in this study had experienced an acute, severe, neurological deficits. All of the patients enrolled in our study had either paraplegia, hemiplegia, or quadriplegia. Additionally, two patients were aphasic (had impairment of language function), and one patient was in coma. All patients had failed treatment with intravenous methylprednisolone, and there was a two-week waiting period following the first administration of intravenous methylprednisolone before patients were deemed eligible for enrollment. Patients were separately randomized in group A (patients with MS) and group B (patients with other CNS inflammatory demyelinating disease). Four patients who were enrolled had ATM with no prior episodes that would make one suspicious of MS. The outcome measure was simple and robust, namely moderate-to-marked improvement in the neurological deficit as determined by the blinded neurologist examiners. A number of clinical scales were used to further document and verify the consistency with which the primary outcome was determined. In this study, patients who received “sham” exchange had exactly the same procedures performed to their blood, except that instead of replacing the separated plasma with albumin, the plasma and cells were remixed and returned to the patients unchanged. After the first two weeks of treatment, patients who had not improved crossed over to the opposite treatment for a further two weeks.

The results of this study were reported in September, 1999, and published in the December, 1999 issue of *Annals of Neurology*.

The study conclusively proved a benefit of plasma exchange; 42.1% (8 of 19 patients) who received true plasma exchange experienced moderate-to-marked improvement during treatment compared to 5.9 % (1 of 17 patients) who were receiving sham exchange. Three patients who failed sham treatment in the first treatment period subsequently developed significant improvement after “crossing over” to the active treatment during the second treatment period. There was no instance of similar improvement after crossing over from active to sham treatment. The benefits of plasma exchange were sustained on follow-up. However, several patients with MS did experience recurrent attacks in follow-up.

Of the four patients who were enrolled with a diagnosis of ATM, one patient experienced dramatic improvement, two failed, and one died of a rare complication of heparin

treatment during the first treatment period. The latter patient had received sham treatment and had not had the opportunity to be exposed to the active treatment in the second treatment period. Of 13 patients enrolled with a targeted neurological deficit of paraplegia, 4 out of 13 experienced moderate-to-marked improvement in this study.

Overall, plasma exchange was well tolerated. Approximately half of the patients enrolled in the study required a central intravenous catheter inserted through a major vein in the neck, but this was accomplished without complication in each case. As noted, one patient died of a rare complication of heparin treatment, and one other patient died while receiving sham treatment due to progression of her neurological deficit.

On one hand, we believe that we have proven beyond a reasonable doubt that plasma exchange is effective in this setting. On the other hand, we note that somewhat under 50% of patients who received sham exchange improved. Furthermore, we studied, exclusively, patients with acute, severe deficits of recent onset (less than three months of the onset of neurological deficit), and we studied only patients who had previously received intravenous methylprednisolone 500 mg per day or equivalent high-dose corticosteroid treatment and had failed.

Since the completion of this study, we have analyzed our entire patient experience in 59 patients treated for acute, severe neurological deficits due to central nervous system demyelinating disease with plasma exchange. The response rate in patients treated within and outside of the confines of the study was similar (approximately 42%) and has not varied over the past 15 years since the first such treatment was performed at Mayo Clinic. Although no statistically significant differences were evident, the best results were encountered in patients with ATM in the setting of neuromyelitis optica (60% response; 6 of 10 patients). The response rate in patients with isolated ATM was 33.3% (2 of 6 patients).

We advocate treatment with plasma exchange in patients in the setting on acute severe attack of idiopathic inflammatory demyelinating disease, unresponsive to corticosteroids. Alternative causes of this syndrome (e.g. vascular, infectious, trauma, neoplastic) should be considered and excluded, preferably before initiation of plasma exchange when feasible. Further controlled clinical trials would be desirable to confirm these results.