

Abstract

Plasma exchange to treat steroid-unresponsive attacks of severe demyelinating disease

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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 which effects 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 might also respond.

Acute transverse myelitis in its prototypic form is distinguishable from attacks of myelitis resulting from multiple sclerosis. Acute transverse myelitis typically follows viral infection and results in relatively severe, symmetrical involvement of strength, sensation, and bowel and bladder function. Typically, there are longitudinally extensive lesions with significant cord swelling on the MRI scans of patients with acute transverse myelitis. 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. However, it is important to emphasize that both are acute inflammatory demyelinating diseases of the central nervous system. The etiology is unknown for either condition, and it is unclear whether the clinical distinctions noted above 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.

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. While the results of plasma exchange in patients with progressive forms of MS remain controversial, there is no clear evidence for benefit. 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, there was a clear need for a prospective, randomized study with excellent masking of the treatment from both physician and patient to circumvent the problems of bias.

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. 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 inflammatory demyelinating disease. Four patients who were enrolled had acute transverse myelitis 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.

The results of this study will be reported at the first joint meeting of the European and American Committees for Treatment and Research in MS (ECTRIMS/ACTRIMS) on September 17, 1999. The full results of this study will be published shortly in the *Annals of Neurology*.

The study conclusively proved a benefit of plasma exchange; 42.1% of patients who received true plasma exchange experienced moderate-to-marked improvement during treatment compared to 5.9% of patients who were receiving sham exchange. 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. 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 acute transverse myelitis, 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 placement of a central intravenous line 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 or equivalent high-dose corticosteroid treatment and had failed. We advocate treatment with plasma exchange in patients in this setting only. At this point, we feel that it is premature to extend the use of plasma exchange to any other patients with inflammatory demyelinating diseases unless further evidence emerges suggesting that the indications are broader than those that we studied.

Biographical Sketch

Dr. Brian G. Weinshenker is a Professor of Neurology at the Mayo Clinic. Doctor Weinshenker was born in Winnipeg, Canada and completed medical school at the University of Manitoba. He trained in internal medicine at the University of Manitoba, and subsequently in neurology at the University of Minnesota. He completed a research fellowship at the University of Western Ontario in London, Ontario in neuroimmunology under the mentorship of Dr. George Ebers. Doctor Weinshenker was Assistant Professor of Neurology at the University of Ottawa between 1988 and 1992, and subsequently, he moved to Rochester, Minnesota, taking his current position at the Mayo Clinic.

Doctor Weinshenker's practice heavily concentrates on multiple sclerosis and related inflammatory demyelinating diseases. He has a special interest in Devic's disease (neuromyelitis optica). Doctor Weinshenker conducts research into genetic variants that contribute to the severity of multiple sclerosis. He is an expert in the natural history of multiple sclerosis and how natural history can be utilized to design clinical trials in multiple sclerosis.

Doctor Weinshenker has recently completed a four-year clinical trial sponsored by the National Institutes of Health to evaluate the effectiveness of plasma exchange as a treatment for acute, severe, inflammatory demyelinating diseases of the central nervous system.