Plasma Exchange in Neuroimmunological Disorders

Part 1: Rationale and Treatment of Inflammatory Central Nervous System Disorders

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Plasma exchange is a well-established therapeutic procedure commonly used in many neurological disorders of autoimmune etiology. It is thought that the beneficial effects of plasma exchange occur through the elimination of pathognomonic inflammatory mediators, including autoantibodies, complement components, and cytokines. In various neurological disorders, randomized controlled studies have demonstrated the efficacy of plasma exchange (eg, in Guillain-Barré syndrome and other forms of immune neuropathies). Although widely used, the potential benefit of plasma exchange in the treatment of multiple sclerosis, myasthenia gravis, and Lambert-Eaton syndrome is less clear.

Plasma exchange has become an established therapeutic procedure in neurological practice for numerous pathologic conditions. In fact, the latest review of plasma exchange use by the Canadian Apheresis Group indicates that 3 neurological disorders (myasthenia gravis, Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy) are among the 5 most frequent indications for this therapy. Most neurological disorders that are treated with plasma exchange are associated with presumed aberrant humoral immune responses, including myasthenia gravis, Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy. In some of these disorders, the efficacy of plasma exchange has already been demonstrated in randomized controlled clinical trials, whereas its role in the treatment of other diseases remains less clear.

This part of our review series outlines the rationale and technical aspects of plasma exchange. We also define its current role in the treatment of inflammatory disorders of the central nervous system (CNS).

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This review will assess and analyze information on relevant randomized controlled studies that provide the basis for the use of plasma exchange in neurological disorders. In the first part of this series, we will review the potential mechanisms of action of plasma exchange and the technical aspects of the procedure and will focus on its current role in the treatment of inflammatory disorders of the CNS. To rate the quality of evidence of specific clinical studies, a rating system was adopted from the report of assessment of disease-modifying therapies in multiple sclerosis (MS) of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines (Table 1).

MECHANISMS OF ACTION AND PROCEDURE OF PLASMA EXCHANGE

Therapeutic plasma exchange constitutes an extracorporeal blood purification technique designed to remove large molecular weight particles from plasma. The removal of circulating autoantibodies, immune complexes, cytokines, and other inflammatory mediators is thought to be the principal mechanism of action. Antibodies against self have been identified in various neurological disorders, including antibodies against nicotinic acetylcholine receptor in myasthenia gravis, antibodies against...
Table 1. Ratings of Recommendation and Quality of Evidence*

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<tr>
<th>Rating of Recommendation</th>
<th>Quality of Evidence</th>
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<tr>
<td>Type A: Established as effective, ineffective, or harmful for the given condition in the specified population. Requires ≥1 convincing class I study or ≥2 convincing class II studies.</td>
<td>Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population. Requires: (a) Primary outcomes clearly defined. (b) Exclusion and inclusion criteria clearly defined. (c) Adequate accounting for dropouts and crossovers, with numbers sufficiently low to have minimal potential for bias. (d) Relevant baseline characteristics are presented and are substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.</td>
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<td>Type B: Probably effective, ineffective, or harmful for the given condition in the specified population. Requires ≥1 convincing class I study or ≥2 convincing class II studies.</td>
<td>Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets (a) through (d) above, or a randomized controlled trial in a representative population that lacks class I criteria.</td>
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<td>Type C: Possibly effective, ineffective, or harmful for the given condition in the specified population. Requires ≥1 convincing class II study or ≥2 convincing class III studies.</td>
<td>Class III: All other controlled trials, including well-defined natural history controls or patients serving as own controls, in a representative population in which outcome is independently assessed or independently derived by objective outcome measurement.</td>
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<tr>
<td>Type U: Data inadequate or conflicting given current knowledge; treatment is unproven.</td>
<td>Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.</td>
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P/Q-type voltage-gated calcium channels in Lambert-Eaton syndrome, and anti-Yo antibodies in MS. Cytokines, including chemokines and complement, are other potentially injurious molecules that may be removed by plasmapheresis. Complete removal of pathogenic antibodies is impossible to achieve. Because of a slow equilibration of large macromolecules between the vascular space and the interstitium, the rate of removal can be expressed as a first-order kinetic. With the use of replacement solutions, the exchange of a single volume of plasma will lower the level of a specific macromolecule by 50% to 60%. Similarly, an increase to 1.4 plasma volumes will lower plasma levels by 75%.18

**TECHNICAL CONSIDERATIONS**

Therapeutic plasma exchange is based on the separation of plasma from the blood's cellular elements. This can be achieved with centrifugation devices or with permeable blood filters. During continuous or intermittent centrifugation, blood components separate because of differences in density. In membrane ultrafiltration, the separation is according to molecular size. Plasma filter membrane pores are up to 0.2 µm in diameter (approximately 30 times the diameter of pores in conventional high-flux hemofilter membranes), allowing the removal of substances up to a molecular weight of 3 × 10^6 Da, which includes immunoglobulins, immune complexes, complement factors, lipoproteins, and endotoxin. At large filtrate production rates, an extent of hemocoagulation is achieved that may predispose to premature clotting of the filter. Therefore, blood flow rates requiring a central venous access are usually necessary. Furthermore, the degree of anticoagulation required to prevent clotting is somewhat higher than that needed in hemodialysis patients. Often, systemic heparinization is used for anticoagulation. When centrifugation techniques are applied, the minimum blood flow is generally lower, allowing the use of a peripheral venous access. Citrate anticoagulation instead of a heparin pump is an integrated part of many technical devices. Centrifugal plasmapheresis removes all nonsolid elements from the blood. However, compared with membrane filtration, the loss of cellular elements and especially platelets is unavoidable. Net clearance of a substance by centrifugation is equal.
to be achieved. After adsorption, the cellular blood components and plasma are combined and reinfused. This technique has already been used in different neurological diseases, including MS and myasthenia gravis.

Figure. Hypothetical scheme of the humoral immune response in multiple sclerosis. Antibodies against myelin proteins may cause demyelination and subsequent axonal damage. Other humoral factors that may contribute to the pathogenesis include cytokines, metalloproteinases (MMPs), and complement (Compl). Abs indicates antibodies; AM, adhesion molecules; APC, antigen presenting cell; B, B-cell; BBB, blood-brain barrier; C5b-9, complement 5b-9; CNS, central nervous system; IL, interleukin; LN, lymph node; Mø, macrophage; and T, T cell.

ADVERSE EFFECTS OF PLASMA EXCHANGE

Possible complications related to the use of central venous access, anticoagulation, or replacement fluids have been detected in subgroups of patients with MS. These antibodies may mediate injury by complement fixation or linking with innate immune effector cells such as macrophages. Berger et al demonstrated that antibodies in serum samples of patients with a clinically isolated syndrome are predictive of early conversion to clinical definite MS. While clearly immunoglobulins are synthesized intrathecally, these findings along with others suggest that at least part of the humoral response in MS is derived systemically from the blood. However, no major therapeutic effect of plasma exchange can be expected once antibodies are deposited in situ in CNS lesions. The role of plasma exchange in the management of patients with progressive forms of MS remains unclear.

Multiple sclerosis is a multifocal inflammatory disease of the CNS, characterized by chronic inflammation, demyelination, axonal damage, and subsequent gliosis. Current concepts of its pathogenesis assume that in genetically susceptible individuals potentially self-reactive T cells are activated in the immune system, home onto the CNS, and may initiate tissue damage via release of inflammatory cytokines, stimulation of B cells and macrophages, and activation of the complement system. Recently, there has been a revival of interest in the role of humoral factors in the pathologic process (Figure). Antibodies against myelin basic protein and myelin oligodendrocyte glycoprotein have been detected in subgroups of patients with MS. These antibodies may mediate injury by complement fixation or linking with innate immune effector cells such as macrophages. Berger et al demonstrated that antibodies in serum samples of patients with a clinically isolated syndrome are predictive of early conversion to clinical definite MS. While clearly immunoglobulins are synthesized intrathecally, these findings along with others suggest that at least part of the humoral response in MS is derived systemically from the blood. However, no major therapeutic effect of plasma exchange can be expected once antibodies are deposited in situ in CNS lesions. The role of plasma exchange in the management of patients with progressive forms of MS remains unclear.

The first randomized, controlled, double-blind trial of plasmapheresis, by Khatri and coworkers among 54 patients with a progressive form of MS, showed a clinical benefit after 5 months in the plasma exchange group compared with the sham treatment group. A larger 3-armed trial of the Canadian Cooperative Multiple Sclerosis Study Group randomized 168 patients with chronic progressive MS to receive daily cyclophosphamide and oral prednisone (n=55), daily cyclophosphamide and prednisone every other day for 22 weeks and weekly plasma exchange for 20 weeks (n=57), or placebo medications and sham plasma exchange (n=56). All patients were followed up for at least 12 months. The study showed no ef-
ficiency in the outcome measure, defined as Expanded Disability Status Scale progression by at least 1 point (treatment failure) at 6 months and mean change in Expanded Disability Status Scale at 12 months. The long-term benefit of plasma exchange in the treatment of chronic progressive forms of MS remains elusive, and plasma exchange cannot be recommended (type A recommendation [Table 1]).

A weakness of most studies of plasma exchange in chronic progressive forms of MS is the lack of evaluation of magnetic resonance imaging activity, nowadays the most important surrogate marker in the assessment of potential therapeutic drug effects in MS. A small randomized, single-blind, crossover study of 11 patients with secondary progressive MS investigated the effect of plasma exchange in combination with azathioprine on metrics of magnetic resonance imaging activity (gadolinium-enhancing lesions and new enhancing lesions). No significant differences were found with regard to this outcome measure, perhaps confirming the disappointing results in the earlier larger trials. The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines concluded that plasma exchange “is of little or no value in the treatment of progressive MS.”

Acute Forms of CNS Demyelinating Diseases

In contrast to chronic progressive MS, plasma exchange may be useful in acute exacerbations of MS. The largest trial to study the effectiveness of plasma exchange in acute exacerbations in MS dates back to 1989. In this randomized, controlled, double-blind trial, 116 patients were assigned to receive 11 treatment cycles of plasma exchange or sham exchange during 8 weeks. Corticotropin (ACTH) and cyclophosphamide were given to patients in both groups as indicated. During the treatment period, a greater clinical improvement was observed in the plasma exchange group. Unfortunately, the long-term effect at 12 months was less clear (class I evidence [Table 1]).

Weinshenker and coworkers demonstrated in a randomized, controlled, double-blind trial the beneficial effects of plasma exchange in acute forms of CNS demyelinating diseases. Twenty-two patients with MS or other demyelinating diseases (transverse myelitis, Marburg variant of MS, acute disseminated encephalomyelitis, neuromyelitis optica, and focal cerebral demyelination) failing to respond to high-dose corticosteroids received 7 cycles of plasma exchange or sham treatment. Patients who showed no clinical improvement on day 14 were crossed over to the other trial arm. In this study, plasma exchange was superior to sham treatment in the primary outcome measure, which was defined as improvement of a target neurological deficit (coma, aphasia, hemiplegia, paraplegia, or quadriplegia) (class I evidence [Table 1]). Although the number of patients in this trial was small, plasma exchange is now regarded as a treatment option for patients with acute fulminant CNS demyelinating diseases who fail to improve with high-dose corticosteroid treatment (type A recommendation). However, further studies with a larger number of patients are required to examine the optimal number of treatment cycles.

Recently, Keegan and colleagues retrospectively reviewed the outcome after plasma exchange treatment in 19 patients who underwent brain biopsy before treatment initiation. This cohort was stratified according to the immunopathologic pattern of MS lesions, as described by Lucchinetti et al. Keegan and coworkers demonstrated that there was a strong correlation between the beneficial effects of plasma exchange therapy and the immunopathologic pattern II, which is characterized by antibody-mediated and complement-mediated demyelination. This study underlines the importance of identifying patient subgroups that are more likely to benefit from plasma exchange.

Favorable effects of plasma exchange were also seen in 2 recent retrospective case series of patients with severe optic neuritis and severe demyelinating events of the CNS. Despite limitations in the study design (no control group), these results encourage further evaluation of the role of plasma exchange in patients with severe demyelinating events.

Rasmussen Encephalitis

Rasmussen encephalitis is a rare disorder of childhood onset characterized by intractable focal seizures, hemiplegia, dementia, and unilateral brain dysfunction. Cumulative evidence suggests that Rasmussen encephalitis has an autoimmune etiology. Humoral factors may be involved in the pathogenesis of the disease. Pathologic hallmarks are inflammation and glialosis in the affected cerebral hemisphere. Focal disruption of the blood-brain barrier, perhaps caused by focal seizures, may allow the access of pathologic humoral factors to brain tissue. The subsequent local inflammation perpetuates the vicious circle of neural injury, focal seizure, and transient disruption of the blood-brain barrier. Antibodies have been detected in serum samples of patients with Rasmussen encephalitis that are directed against the glutamate receptor GluR3. A major pathogenic role of anti-GluR3 antibodies has been challenged because they have also been identified in patients with focal epilepsy and (in lower frequency) in other neurological diseases, and their contribution remains unresolved. Cytotoxic CD8 T cells have been identified in the brains of affected individuals with Rasmussen encephalitis, and it has been suggested that their direct assault on neurons underlies disease pathogenesis.

To our knowledge, no randomized controlled trial has examined the effectiveness of plasma exchange in Rasmussen encephalitis; therefore, evidence is categorized as class IV (Table 1). Single case reports have demonstrated marked clinical improvement and decreasing immunoreactivity against GluR3 in serum samples of treated patients; thus, the clinical value of plasma exchange is uncertain (type U recommendation). Andrews and coworkers reported in a small case series the rapid resolution of intractable seizures in some patients with plasma exchange (Table 2). Therefore, status epilepticus, a complication frequently observed in Rasmussen encephalitis, might be an additional clinical indication for plasma exchange.

Paraneoplastic Disorders of the CNS

Paraneoplastic disorders of the CNS, including cerebellar degeneration, paraneoplastic encephalomyelitis, stiff-person syndrome, and others, are rare neurological disor-
Clinical symptoms of this rare disorder are muscle rigidity, gait ataxia, and episodic autonomic instability. There are no randomized controlled studies of the use of plasma exchange, to our knowledge. However, retrospective studies and case series did not show any substantial benefit of clinical and serological parameters51-53 (class IV, type U recommendation [Table 1]).

In patients with stiff-person syndrome, high titers of antibodies against glutamic acid decarboxylase have been demonstrated in serum samples and cerebrospinal fluid. Clinical symptoms of this rare disorder are muscle rigidity and spasm of axial and limb musculature. Although we are unaware of any randomized controlled trial of the utility of plasma exchange in stiff-person syndrome, there are some anecdotal reports with beneficial results54-57 (class IV, type U recommendation [Table 1]).

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Author Contributions: Study concept and design: Hartung, Hetzel, and Stuve. Acquisition of data: Stuve. Analysis and interpretation of data: Lehmann, Hartung, Hetzel, Stuve, and Kieseier. Drafting of the manuscript: Lehmann, Hartung, and Stuve. Critical revision of the manuscript for important intellectual content: Hartung, Hetzel, and Kieseier. Obtained funding: Kieseier. Administrative, technical, and material support: Hartung and Stuve. Study supervision: Hetzel and Stuve.

Table 2. Summary of Selected Trials of Plasma Exchange for Inflammatory Disorders of the Central Nervous System

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Khatri et al,56 1985</td>
<td>PE (20×) + prednisone + cyclophosphamide vs sham treatment (20×) + prednisone + cyclophosphamide, double-blind</td>
<td>54</td>
<td>Better clinical improvement (EDSS) in PE group.</td>
</tr>
<tr>
<td>Canadian Cooperative Multiple Sclerosis Study Group,34 1991</td>
<td>Intravenous cyclophosphamide + oral prednisone daily (n = 55) vs oral cyclophosphamide daily and prednisone every other day (22 wk) vs PE (20 wk) (n = 57) vs placebo and sham PE (n = 56), single-blind</td>
<td>168</td>
<td>No significant differences in primary end point (rates of treatment failure as worsening of evaluating neurologist’s assessment of EDSS by ≥1.0 on two 6-mo examinations) (19 [34.5%] vs 18 [31.6%] with plasma exchange vs 16 [28.6%] with placebo).</td>
</tr>
<tr>
<td>Weiner et al,36 1989</td>
<td>PE (11×) + corticotropin + oral cyclophosphamide vs sham PE + corticotropin + oral cyclophosphamideamide, double-blind</td>
<td>116</td>
<td>PE patients had moderate improvement at 2 wk. PE patients with relapsing or remitting disease had significantly marked improvement at 4 wk. No clear long-term benefits.</td>
</tr>
<tr>
<td>Weinschenker et al,37 1999</td>
<td>PE vs sham treatment, double-blind, crossover to alternative treatment in case of no improvement</td>
<td>36</td>
<td>Significant better improvement in primary outcome (target neurological deficit) in 42% of PE population vs 5.9% of sham group (P = .01).</td>
</tr>
<tr>
<td>Ruprecht et al,41 2004</td>
<td>PE</td>
<td>10</td>
<td>Improvement of visual acuity.</td>
</tr>
<tr>
<td>Andrews et al,43 1996</td>
<td>PE, no control group</td>
<td>4</td>
<td>Transient improvement of 3 patients; 1 marginally improved.</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS, Expanded Disability Status Scale; PE, plasma exchange.