Plasma Exchange in Neuroimmunological Disorders

Part 2. Treatment of Neuromuscular Disorders

Helmar C. Lehmann, MD; Hans-Peter Hartung, MD; Gerd R. Hetzel, MD; Olaf Stüve, MD; Bernd C. Kieseier, MD

Plasma exchange is a well-established therapeutic procedure commonly used in many neurological disorders of autoimmune etiology. In this second part of our review, we assess the role of plasma exchange in the treatment of neuromuscular disorders. In Guillain-Barré syndrome and other immune-mediated neuropathic disorders, randomized controlled trials have demonstrated the therapeutic efficacy of plasma exchange. Myasthenia gravis and Lambert-Eaton syndrome represent neuromuscular disorders where plasmapheresis might be of potential efficacy.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) represents a spectrum of neuropathic disorders, including classic acute inflammatory demyelinating polyneuropathy, axonal variants with or without sensory involvement (acute motor and sensory axonal neuropathy and acute motor axonal neuropathy, respectively), and clinical variants such as Miller Fisher.1,2 Aberrant humoral and cellular immune response systems are involved in the pathogenesis of GBS. Molecular mimicry, in which epitopes incidentally shared by microbial antigens and nerve structures elicit an autoreactive T-cell or B-cell response in the wake of an infective illness, may trigger the autoimmune process.3 In about 60% of cases, GBS follows closely an infection, most frequently caused by the microbiological agent Campylobacter jejuni.3,5 Activated T cells migrate across the blood-nerve barrier and are reactivated in situ when their autoantigen is appropriately displayed by macrophages along with major histocompatibility complex II products and co-stimulatory molecules. Autoantibodies crossing the blood-nerve barrier en passant with T cells or accessing target structures directly at the most proximal or distal parts of the nerve contribute to the inflammatory process by antibody-dependent cytotoxicity and activation of complement (Figure 1).2 A large variety of antibodies against different glycolipids, including GM1, GD1a, and GQ1b, among others, have been described.9

Plasma exchange is well established as treatment in GBS.7 Its therapeutic use over and above supportive care has been demonstrated in 2 large randomized, controlled, nonblinded, multicenter trials (class I evidence). In the first study, 245 patients were included and received plasma exchange or conventional supportive therapy8 (Table). Clinical outcomes, that is, time to improve 1 clinical grade and time to independent walking, were assessed at 4 weeks and 6 months. In the study of the French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome,9 220 patients were included and received plasma exchange or conventional supportive therapy (Table). Clinical outcomes, that is, time to improve 1 clinical grade and time to independent walking, were compared with 111 patients defined as the control group. Substantial benefit was documented for the primary end point, that is, time to recover the ability to ambulate with assistance, and in secondary factors such as the reduction of the proportion of patients who needed assisted mechanical ventilation, a more rapid time of onset of motor recovery, and clinical factors such as time to walk with and without assistance (Table).9 The same group reported also the long-term ben-

Author Affiliations: Departments of Neurology (Drs Lehmann, Hartung, and Kieseier) and Nephrology (Dr Hetzel), Heinrich Heine University of Düsseldorf, Dusseldorf, Germany; and Department of Neurology, The University of Texas Southwestern Medical Center at Dallas (Dr Stüve).
Figure 1. Humoral immune response in inflammatory neuropathic disorders. Autoantibodies crossing the damaged blood-nerve barrier (BNB) or produced by local B cells (B) causing demyelination by complement activation and macrophage (Mφ)-dependent cytotoxicity. Other pathological effects include interference with nerve conduction at the nodes of Ranvier or alteration of neuromuscular transmission. Abs indicates antibodies; C jejuni, Campylobacter jejuni; IL, interleukin; NMJ, neuromuscular junction; T, T cells.

benefit in the plasma exchange population as recovery of full muscle strength after 1 year in 71% of patients compared with 52% of subjects in the control group. A 1997 study addressed the optimal number of plasma exchange sessions in the treatment of GBS. In this randomized, controlled, nonblinded trial, 556 patients were included and randomized to 3 groups according to degree of disability. Patients with mild disability underwent either 0 or 2 plasma exchange sessions, those with moderate disability underwent 2 or 4 sessions, and those with severe disability underwent 4 or 6 sessions. It could be demonstrated that 2 vs 0 plasma exchange sessions in patients with mild disability and 4 vs 2 plasma exchange sessions in patients with moderate disability were more beneficial. More than 4 treatments did not yield additional benefit in patients receiving mechanical ventilation in the group with severe disability. This study provided important guidelines as to the number of plasma exchange sessions to be performed in patients with different degrees of disability (class I evidence) (Table). Also, patients with mild symptoms can benefit from plasma exchange, whereas more than 4 plasma exchange sessions are not indicated in patients with severe symptoms.

Based on several studies of class I evidence, plasma exchange has been established as effective treatment in the therapy of GBS (type A recommendation), which is reflected in the last updated review from the Cochrane Collaboration. Plasma exchange is most beneficial when started within 7 days of disease onset, but is also efficacious when started after 30 days.

PLASMAPHERESIS VS INTRAVENOUS IMMUNOGLOBULIN THERAPY

Compared with the other available therapeutic approach in GBS, that is, intravenous immunoglobulin therapy (IVIG), plasma exchange is considered equally efficacious (class I evidence). This statement is based on the results from 2 trials. The first randomized, controlled, non-blinded study included 150 patients with GBS assigned to either undergo plasma exchange or receive IVIG. Primary outcome was assessed after 4 weeks as motor recovery by at least 1 grade on the predefined 7-point scale of motor function (Hughes scale). In the IVIG group, 53% of patients demonstrated improvement compared with 34% of patients in the plasma exchange group. The authors concluded that IVIG is at least as effective as plasma exchange in the treatment of GBS and is associated with a lower rate of complications. A randomized controlled trial of 383 patients with GBS compared the relative efficacy of plasma exchange, IVIG, and IVIG after plasma exchange. Primary outcome measure was also improved at 4 weeks by at least 1 grade on a 7-point scale of motor function. No significant differences in primary and secondary outcome measures were reported. In conclusion, plasma exchange and IVIG are of at least equal efficacy in the treatment of GBS (type A recommendation). The combined treatment of plasma exchange and IVIG does not seem to have an additional benefit.

PLASMAPHERESIS VS CEREBROSPINAL FLUID FILTRATION (LIQUORPHERESIS)

During cerebrospinal fluid filtration (liquorpheresis), cerebrospinal fluid is automatically withdrawn through a spinal catheter and reinfused. During 1 session, 150 to 250 mL of cerebrospinal fluid is cycled, and this is repeated 5 to 15 times. One randomized controlled study compared liquorpheresis with plasma exchange in 37 patients with GBS. No differences in the primary outcome variable (improvement within 4 weeks) and several secondary outcome measures were observed. The authors concluded that the 2 treatments are equally efficacious. The study raised several concerns. First, the trial may have been underpowered for the size of the patient cohort required to show a difference between the 2 study groups. Another weakness of the unblinded study was that important outcome measures used in previous trials, such as the median time to improvement by 1 functional grade, were not assessed. The study, therefore, is rated only as a trial of class II evidence (type C recommendation).

IMMUNOADSORPTION IN GBS

By use of immunoadsorption, selective removal of immunoglobulin fractions can be achieved. In GBS, some small retrospective studies compared efficacy and adverse effects of immunoadsorption with plasma exchange and found no major differences. However, the selective elimination of presumed pathogenic antibodies by use of specifically designed immune-affinity columns might be a future approach to optimize this therapeutic procedure and minimize adverse effects. Recently, Willison et al demonstrated the “proof of principle” experimentally. Anti–GQ1b antibodies could be immunodepleted in serum samples from patients with the Miller Fisher variant of GBS by using a synthetic trisaccharide as specific epitope for anti–GQ1b antibodies.
therapy or IVIG or plasma exchange, followed by long-term treatment. Treatment usually consists of either corticosteroids or immunosuppressive therapy, which includes plasma exchange (PE), intravenous immunoglobulin (IVIG), and other therapies. IVIG and PE are used to eliminate factors from the blood that may be causing the disease and to provide temporary replacement of antibodies. IVIG is a preparation of pooled human immunoglobulin prepared from pooled plasma of normal donors. PE is the exchange of plasma for replacement plasma, which is usually fresh frozen plasma (FFP) or albumin.

**Chronic Inflammatory Demyelinating Polyneuropathy**

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired, immune-mediated, peripheral neuropathy. Its response to immunosuppressive therapy and its clinical resemblance to GBS suggest an autoimmune origin of the disease. 22-24 The presence of autoantibodies against various proteins and glycolipids of the peripheral nerve in samples of serum and cerebrospinal fluid from patients with CIDP 22-24 may provide a rationale for the therapeutic use of plasma exchange. Treatment usually consists of either corticosteroid therapy or IVIG or plasma exchange, followed by long-term treatment. Treatment usually consists of either corticosteroids or immunosuppressive therapy, which includes plasma exchange (PE), intravenous immunoglobulin (IVIG), and other therapies. IVIG and PE are used to eliminate factors from the blood that may be causing the disease and to provide temporary replacement of antibodies. IVIG is a preparation of pooled human immunoglobulin prepared from pooled plasma of normal donors. PE is the exchange of plasma for replacement plasma, which is usually fresh frozen plasma (FFP) or albumin.

**Table. Summary of Selected Trials for Plasma Exchange in Disorders of the Peripheral Nervous System**

<table>
<thead>
<tr>
<th>Trial/Source</th>
<th>Study Characteristics and Design</th>
<th>No. of Patients</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guillain-Barré Syndrome</strong></td>
<td>PE vs supportive care; single blinded</td>
<td>245</td>
<td>Improvement at 4 wk, time to improve 1 clinical grade, 3.5 mo to independent walking, and outcome at 6 mo in the PE group.</td>
</tr>
<tr>
<td>French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome</td>
<td>PE (4×) with albumin (n = 57) vs PE (4×) with fresh frozen plasma (n = 52) vs no PE (n = 111); nonblinded</td>
<td>220</td>
<td>Shorter time to recovery walking with assistance (30 vs 44 d; P &lt; .01) in PE group; fewer patients requiring assisted ventilation, shorter time to onset of motor recovery; no differences between PE groups.</td>
</tr>
<tr>
<td>French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome</td>
<td>3 Groups: mild disability, 0 vs 2 PE sessions; moderate disability, 2 vs 4 PE sessions; severe disability, 4 vs 6 PE sessions; nonblinded</td>
<td>556</td>
<td>Two PE sessions more effective than 0 sessions for time to onset of motor recovery (4 vs 8 d; P &lt; .001) in group with mild disability; 4 PE sessions superior to 2 PE sessions for time to walk with assistance (20 vs 24 d; P = .04) in group with moderate disability; no difference between 4 and 6 PE sessions in group with severe disability.</td>
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<tr>
<td>Dutch Guillain-Barré Study Group</td>
<td>PE (5×) vs IVIG (0.4 g/kg per day, 5 d); nonblinded, bias controlled</td>
<td>150</td>
<td>Improvement in NDS (41 vs 27 d; P = .05); both treatments are of equal efficacy, but IVIG may be superior.</td>
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<tr>
<td>Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group</td>
<td>PE (5×) (n = 121) vs IVIG (0.4 g/kg/d, 5 d) (n = 130) vs PE (5×) + IVIG (0.4 g/kg/d, 5d) (n = 132); single blinded</td>
<td>383</td>
<td>No significant difference in major outcome measure (improvement on disability scale after 4 wk) or secondary outcome measures (time to recovery of unaided walking and time to discontinuation of mechanical ventilation).</td>
</tr>
<tr>
<td>Wollinsky et al</td>
<td>Liquorapheresis vs PE; nonblinded, crossover to alternative treatment in case of no improvement</td>
<td>37</td>
<td>Clinical improvement after 28 d similar in both groups; no significant differences in secondary outcome measures.</td>
</tr>
<tr>
<td><strong>Chronic Inflammatory Demyelinating Polyneuropathy</strong></td>
<td>PE (6×) vs sham treatment; double blinded</td>
<td>29</td>
<td>Significantly better outcome in measurements of nerve conduction (total, motor, proximal, velocity, and amplitude) in PE group.</td>
</tr>
<tr>
<td>Dyck et al</td>
<td>PE (10×) vs sham treatment; double blinded, crossover</td>
<td>18</td>
<td>Significant improvement in PE group in clinical outcome measures (NDS) and in most electrophysiological measurements.</td>
</tr>
<tr>
<td>Dyck et al</td>
<td>PE (7×) vs IVIG (0.4 g/kg, 1 per 3 wk, then 0.2 g/kg, 1 per 3 wk); single blinded, crossover in case of no improvement or worsening</td>
<td>20</td>
<td>No significant differences between the 2 groups in clinical outcome (NDS) and electrophysiological parameters.</td>
</tr>
<tr>
<td><strong>Paraproteinemic Polyneuropathy</strong></td>
<td>PE (6×) vs sham treatment; double blinded</td>
<td>39</td>
<td>Marked improvement in NDS (46.3 to 58.3 in PE group, 60.5 to 62.5 in sham treatment group; P = .02); no differences in electrophysiological parameters (summed motor nerve conduction velocity, sensory nerve action potentials); more benefit in the IgG and IgA gammopathy subgroups compared with the IgM gammopathy population.</td>
</tr>
<tr>
<td>Dyck et al</td>
<td>PE (6×) vs sham treatment; double blinded</td>
<td>39</td>
<td>Marked improvement in NDS (46.3 to 58.3 in PE group, 60.5 to 62.5 in sham treatment group; P = .02); no differences in electrophysiological parameters (summed motor nerve conduction velocity, sensory nerve action potentials); more benefit in the IgG and IgA gammopathy subgroups compared with the IgM gammopathy population.</td>
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<tr>
<td><strong>Myasthenia Gravis</strong></td>
<td>PE 3× (n = 41) vs IVIG (0.4 g/kg) for 3 d (n = 23) vs IVIG (0.4 g/kg) for 5 d (n = 23); nonblinded</td>
<td>87</td>
<td>No difference in the primary outcome measure (variation of MMS) between PE and IVIG groups (+1AT vs +1.5 AT; P = .65); similar efficacy between the IVIG groups.</td>
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Abbreviations: IVIG, intravenous immunoglobulin; MMS, myasthenic muscular score; NDS, neurological disability score; PE, plasma exchange.
term immunosuppression with azathioprine or cyclosporine.7,28-30

Two randomized, controlled, double-blind studies provided class I evidence that plasma exchange is superior to sham treatment in CIDP.31,32 Thus, plasma exchange can be recommended in the treatment of CIDP (type A recommendation). The efficacy of plasma exchange compared with IVIG was investigated in a small crossover, single-blinded study in 20 patients with CIDP. A clinical score and summed compound muscle action potential of motor nerves as electrophysiological parameter served as primary outcome measures. An improvement in the primary outcome measures was documented for both treatments. Statistically significant differences between IVIG and plasma exchange were not noted.33 The patient cohorts in this study were too small to demonstrate a significant difference between the 2 treatments; thus, it is rated as a trial of class II evidence. To date, there are not enough data available to give preferential recommendation to either plasma exchange or IVIG. There is consensus that treatment of CIDP should be tailored to each patient.

PARAPROTEINEMIC NEUROPATHIES

In approximately 10% of patients with idiopathic polyneuropathic disorders, a monoclonal immunoglobulin can be detected in serum or urine.34 Monoclonal gammopathy of undetermined significance is the most frequent form.35 Lymphoproliferative disorders such as Waldenström macroglobulinemia are other monoclonal gammopathies. In approximately 50% of IgM gammopathy–associated neuropathic disorders, antibodies are directed to myelinsporeine.7,28-30 In a randomized, controlled, double-blind trial, Dyck et al37 studied the effectiveness of plasma exchange in the treatment of polyneuropathy associated with monoclonal gammopathy of undetermined significance. Thirty-nine patients were randomly assigned to receive either plasma exchange twice weekly for 3 weeks or sham treatment. Based on its effects on the 2 primary outcome measures, that is, the neuropathy disability score and the summed compound muscle action potentials of motor nerves, a treatment benefit was suggested for plasmapheresis, whereas in secondary end points, that is, nerve conduction velocity and sensory nerve action potentials, no statistically significant differences were found. The study demonstrated, furthermore, that patients with IgG or IgA gammopathy benefit more than those with IgM gammopathy; hence, plasma exchange can be recommended in at least this subgroup of patients (class I evidence, type A recommendation).

To date, the role of plasma exchange in the treatment of neuropathologic disorders associated with lymphoproliferative disorders (eg, POEMS [polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes] syndrome or Waldenström macroglobulinemia) has been studied only in small case series38-40 generating class III evidence, and, in aggregate, its therapeutic value remains unclear (type U recommendation).

MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune-mediated disorder of the neuromuscular junction, clinically characterized by fluctuating muscle weakness and fatigability.31,42 The most common variant of the disease is mediated by circulating autoantibodies against the nicotinic acetylcholine receptor (AChR) or against the muscle-specific receptor tyrosine kinase (MuSK) cause muscle weakness by disturbing neuromuscular transmission. ACh indicates acetylcholine.

The treatment of myasthenia gravis includes thymectomy and use of acetylcholine esterase inhibitors, corticosteroid agents, immunosuppressive agents, plasma exchange, and IVIG.32 Plasma exchange might be useful in myasthenic crisis and in the preoperative and postoperative phases of thymectomy in severe forms of myasthenia gravis.33 It is presumed that elimination of circulating AChR antibodies and other antibodies with different specificities can be detected, for example, antibodies against the muscle-specific receptor tyrosine kinase (Figure 2).30,51

The treatment of myasthenia gravis includes thymectomy and use of acetylcholine esterase inhibitors, corticosteroid agents, immunosuppressive agents, plasma exchange, and IVIG.32 Plasma exchange might be useful in myasthenic crisis and in the preoperative and postoperative phases of thymectomy in severe forms of myasthenia gravis.33 It is presumed that elimination of circulating AChR antibodies and other humoral factors of pathological significance account for the observed beneficial effects of plasma exchange.

While current concepts of the pathogenesis of and clinical experience in myasthenia gravis, which have evolved over more than 2 decades,54-56 have provided a clear rationale for the use of and collectively demonstrated a salutary effect of plasma exchange, there is, to date, no convincing randomized controlled trial to prove short-term benefit in myasthenic crisis or long-term benefit of plasma exchange.27,58 Although the level of evidence is lower than in other neurological disorders (class IV evidence, type U recommendation), the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology90 considered plasma exchange in the preoperative preparation and treatment of myasthenic crisis as established.

A randomized, controlled, 3-armed trial compared plasma exchange with 2 regimens of IVIG in the treatment of acute exacerbations in myasthenia gravis.60 Eighty-seven patients were randomized either to undergo 3 plasma ex-
change sessions or to receive IVIG (0.4 g/kg per day) for 3 or 5 consecutive days. As a primary outcome measure, the change in myasthenic muscular score between randomization and day 15 was chosen. Secondary end points included, among others, the decrease of anti-AChR antibody titers. Clinical improvement was observed in all patients, but no statistically significant difference in the primary end point or in the effect on anti-AChR antibodies between the 2 groups (plasma exchange vs IVIG) was documented. Adverse effects were less frequent in the IVIG group.

**LAMBERT-EATON MYASTHENIC SYNDROME**

Lambert-Eaton myasthenic syndrome (LEMS) is an immune-mediated, presynaptic neuromuscular junction disorder mediated by antibodies against neuronal P/Q-type voltage-gated calcium channels. In about 60% of patients, LEMS is associated with small cell lung carcinoma, but it can also occur outside the context of neoplasia.

To our knowledge, no randomized controlled trial has investigated the benefit of plasma exchange in LEMS, although case series have repeatedly reported an effect on clinical and electrophysiological parameters in patients with LEMS, whether associated with malignancy or not. Newsom-Davis and Murray described 9 patients treated with plasma exchange and immunosuppressive drugs, of whom exhibited improvement in clinical and electrophysiological outcome measures (class IV evidence). A description of 2 patients with LEMS treated with plasma exchange investigated titers of antibodies directed by P/Q-type voltage-gated calcium channels during the clinical course and the therapeutic procedure. Titers decreased after treatment with plasma exchange but returned to baseline levels after 1 week. Accordingly, the authors observed only a temporary clinical improvement after treatment with plasma exchange alone. These findings suggest only transient benefit for patients with LEMS, perhaps caused by the high rate of production of antibodies to the P/Q-type voltage-gated calcium channels. The role of plasma exchange in the treatment of LEMS remains to be further explored (type U recommendation).

**NEUROLOGICAL DISEASES WITH PROVED OR ASSUMED INEFFECTIVENESS OF PLASMA EXCHANGE**

One randomized controlled trial investigated the effect of plasma exchange in the treatment of inflammatory myopathies. In this 3-armed, double-blind study, 39 patients with either dermatomyositis or chronic polymyositis refractory to corticosteroid therapy were enrolled to receive plasma exchange, leukapheresis, or sham treatment in 12 treatment cycles. No statistically significant differences were observed for final muscle strength or functional capacity. Thus, plasma exchange cannot be recommended in the treatment of inflammatory myopathy (class I evidence, type A recommendation).

Amyotrophic lateral sclerosis is characterized by late onset and progressive loss of motor neurons, leading to paralysis and death. Several small studies of plasma exchange were conducted but failed to detect any substantial alteration in the disease course. Therefore, plasma exchange is possibly ineffective (class III evidence, type C recommendation).

Multifocal motor neuropathy is an acquired demyelinating motor neuropathy, clinically characterized by progressive, predominantly distal, and asymmetric limb weakness with only minor or no sensory deficit. Although the pathogenesis is not known, the frequent occurrence of IgM antibodies against GM1 may imply an immune-mediated origin. In contrast to other chronic forms of inflammatory neuropathy, multifocal motor neuropathy usually does not respond to corticosteroid therapy, whereas treatment with IVIG has shown efficacy. Only a few articles about the use of plasma exchange in multifocal motor neuropathy have been communicated. Most of them did not show any improvement in clinical or electrophysiological parameters, and some reported severe clinical worsening (class IV evidence, type U recommendation).

**CONCLUSIONS**

Therapeutic efficacy of plasma exchange in certain neurological conditions, including GBS, CIDP, and paraproteinemic polynuropathic disorders, has been demonstrated in large randomized controlled studies with a high level of evidence. In some of these neurological disorders, plasma exchange is the therapeutic gold standard to which new treatments are compared, whereas in other neurological disorders, the therapeutic value of plasma exchange remains less clear. Despite the long clinical experience and the frequent use of plasma exchange in neurology, there remain important unresolved questions. What is the appropriate number of plasma exchange sessions in a given neurological disorder? Does plasma exchange interfere with other immunosuppressive or immunomodulatory agents? How can adverse effects be averted to enhance safety and tolerability? What is the long-term effect on the clinical disease course and the disturbed network of T cells, B cells, and humoral factors? For almost all current indications in neurology, further studies are necessary to develop plasma exchange as an optimized treatment method.

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Correspondence: Hans-Peter Hartung, MD, Department of Neurology, Heinrich Heine University of Düsseldorf, Moorstrasse 5, 40225 Düsseldorf, Germany (hans-peter.hartung@uni-duesseldorf.de).

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