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Therapeutic Plasma Exchange in Neurology: 2012

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Abstract

In treating neuro-immunological diseases, neurologists have a number of different drugs to choose from ranging from corticosteroids to IVIg to more specific cell based therapies, the latter most frequently from the world of Oncology. In some diseases, therapeutic plasma exchange, a procedure rather than a drug, is used. The most obvious advantage of therapeutic plasma exchange is the usually rapid onset of action presumably due to removal of pathogenic auto-antibodies. In some diseases, a single course of therapeutic plasma exchange is used while in others prolonged treatment with therapeutic plasma exchange is used. This article will review the use of therapeutic plasma exchange in neurology and will draw heavily upon recent consensus statements from the American Society for Apheresis and the American Academy of Neurology and by Cochrane reviews.

Keywords

apheresis; neurologic indications; plasmapheresis; therapeutic plasma exchange; Guillain-Barre syndrome; CIDP; myasthenia gravis

INTRODUCTION

In most major medical centers performing therapeutic plasma exchange (TPE), neurologic use accounts for the majority of procedures. TPE is attractive as the onset of action is usually rapid presumably due to removal of pathogenic auto-antibodies (1). The neurologic diseases in which TPE is used range from central nervous system diseases to peripheral

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nervous system diseases and cover most areas of neurology. While physicians are able to request TPE for almost any patient, guidelines do exist to assist physicians and their patients.

In 2010, The American Society for Apheresis (ASFA) updated its evidence-based review of indications of therapeutic apheresis therapy (2). By co-incidence, the American Academy of Neurology completed its review of plasmapheresis in neurologic disorders the same year although it was published in 2011 (3). Over the last 10 years, the Cochrane collaboration has been performing reviews of plasma exchange in neurologic disorders but doing this for individual diseases rather than the treatment as a whole (see references below).

In general, the different groups came to very similar conclusions using slightly different methods of assessment (Table 1). In this brief review, the conclusions of the three groups are summarized, the different neurologic diseases are discussed, and questions for future research are posed.

MATERIALS AND METHODS

The consensus statements on TPE in neurological disease by the ASFA (2) and AAN (3) were reviewed, as were Cochrane reviews of TPE in chronic inflammatory demyelinating polyradiculoneuropathy (4), Guillain-Barre' syndrome (5), myasthenia gravis (6), Lambert Eaton Myasthenic Syndrome (7), and paraproteinemic polyneuropathies (IgG/IgA and IgM) (89). Results are summarized and compared.

RESULTS

Results are summarized in Table I.

Szczepiorkowski and colleagues reviewed the evidence on 21 separate neurologic diseases (2). They used a two tier grading system. They determined both a category for an indication for apheresis, I thru IV, (see Table 1 in Reference 2) and a grading recommendation, 1A thru 2C, (see Table 3 in Reference 2). Using this methodology, they found that 7 conditions were Category 1 - disorders for which apheresis is accepted as first-line therapy, either as a primary stand-alone treatment or in conjunction with other modes of treatment. These were chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), Guillain-Barre' syndrome (GBS), myasthenia gravis (MG) (moderate-severe), MG (pre-thymectomy), paraproteinemic polyneuropathies (IgG/IgA), paraproteinemic polyneuropathies (IgM), and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and Sydenham's chorea. Disorders for which apheresis was accepted as second-line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment, Category 2, were determined for acute disseminated encephalomyelitis, Lambert-Eaton myasthenic syndrome (LEMS), multiple sclerosis (MS) (acute), Neuromyelitis optica, and Phytanic acid storage disease (Refsum's disease). For the rest, the data was either insufficient to arrive at a conclusion or the data was strong enough to say TPE did not work.

Following the earlier review of TPE in 1996 (10), the AAN undertook a re-review of TPE in neurology (3). Only 10 diseases were re-evaluated as the AAN excluded all conditions for which there was only class IV evidence (retrospective studies, case reports or case series). Two met the highest level as established effective: CIDP and GBS, and two others were considered probably effective: paraproteinemic polyneuropathies (IgG/IgA) and multiple sclerosis (acute relapses). For the rest of the diseases, they were either established ineffective or had insufficient evidence.

The Cochrane Collaboration is organized differently, and so reviews were undertaken on specific diseases rather than on TPE itself. Both CIDP and GBS received the highest ratings (4, 5). For moderate to severe MG, the authors using different terms conclude that TPE is probably effective to use the AAN language (6). For LEMS (7), MG (pre-thymectomy) (6), and paraproteinemic polyneuropathies (IgG/IgA and IgM anti-MAG) (89), the authors concluded there was insufficient evidence to reach a conclusion.

DISCUSSION

Comments on Individual Diseases

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a disorder of the peripheral nervous system in which the primary pathogenesis is a presumed auto-antibody attack on peripheral nerve myelin resulting in weakness, sensory loss and areflexia in typical cases (11). Guidelines for diagnosis and treatment exist to assist clinicians and patients (12). Three first-line treatments have been shown effective in the short-term: TPE, corticosteroids, and IVIg (41314). Most physicians reserve TPE for severe cases or in cases in which the other therapies do not work, but yet the diagnosis seems correct. For most patients, TPE is a short-term treatment usually given for 2–4 weeks and then stopped. For some however, TPE is given long-term. The exact details of TPE, including volumes and scheduling, are usually individualized.

For CIDP, there are a number of unanswered questions. What is the best regimen to give TPE in short-term use? Is the standard method of 5 exchanges over 2 weeks best? Is there a role for TPE induction in CIDP, whether severe or not? These questions would need clinical trials to answer but there may be information available from pooling large experiences across centers.

Guillain-Barre´ Syndrome (GBS) is also a disorder of the peripheral nervous system in which the primary pathogenesis is a presumed auto-antibody attack on peripheral nerve. It is now known there are many forms of the disease (15) but treatment trials have not differentiated between them. Thus all forms of GBS are treated similarly. Like CIDP, GBS results in weakness, sensory loss and areflexia in typical cases. Guidelines for diagnosis and treatment exist to assist clinicians and patients (16, 17). Two first-line treatments have been shown effective - TPE and IVIg (518). In many parts of the world, IVIg has replaced TPE as the primary treatment due to convenience. However, in other parts of the world, TPE remains the primary treatment as IVIg is unavailable. Small volume TPE has also been used with claims of excellent results (personal communications).

A major role for TPE even in centers using IVIg as the first therapy is as “re-treatment” of those who do not “respond” to an initial course of IVIg. However, this has never been studied.

Thus for GBS, unanswered questions exist. Is small volume TPE as effective as full course TPE and IVIg? Is “re-treatment” of those who do not respond to a first course of IVIg effective? Is more prolonged TPE, for example 3 or 4 weeks, better than the standard 5 exchanges over about 2 weeks?

Myasthenia gravis (MG) is the prototypic auto-immune disease in which auto-antibodies against components of the neuromuscular junction result in weakness. The value of TPE in MG has been known for many years (19). With the use of oral immunosuppressants, TPE is mainly reserved for MG crisis and as induction prior to thymectomy. However in recent years, the spectrum of MG has expanded with the discovery of those with anti-MuSK

antibodies (20). This group of MG patients can be very difficult to treat, and many remain dependent on TPE for long periods (21).

For MG, the ASFA and AAN groups have pointed out that better studies are needed in MG to understand the role of TPE both for moderate-severe cases (MG crisis) and as induction prior to thymectomy. In addition, the role of TPE in the anti-MuSK cases should be studied in a multi-center trial.

Paraproteinemic polyneuropathies are an entire topic to themselves. This is a complex and evolving field as the approach to the patient depends on the type of neuropathy (traditionally axonal vs. demyelinating) and the paraprotein. Most of the literature deals with paraproteinemic demyelinating polyneuropathies (PDN) and further breaks these down in those of IgG/IgA type, and those of the IgM type. The IgM are further divided into those with anti-MAG activity and those without anti-MAG activity. Guidelines exist to assist clinicians and patients (22). However, the situation is further complicated by the fact that most of the guidelines deal with monoclonal gammopathies of uncertain significance (MGUS). Those with MGUS IgG/IgA PDN are treated as CIDP above and the same conclusions regarding TPE apply (8). For those with MGUS non-anti-MAG IgM PDN the situation re TPE is less certain (9). For those with MGUS anti-MAG IgM PDN, TPE is not effective as the disease course is quite protracted. We have argued for a strong working relationship between neurology and oncology to maximize treatment and outcomes which may include TPE (23). For those with MGUS non-anti-MAG IgM PDN, the data are that while TPE may have a short-term effect (2), clinicians only use this in severe cases, as again the disease course can be quite protracted.

Lambert-Eaton myasthenic syndrome (LEMS) an auto-immune neuromuscular junction disorder in which the auto-antibody is directed against the voltage gated potassium channel (24) There are two main forms of LEMS: those associated with cancer (paraneoplastic LEMS) and those without cancer (auto-immune LEMS). In both cases, careful screening for cancer including ongoing screening is required. While TPE can be beneficial for severe weakness, IVIg or oral immunosuppressants or both are more frequently used in this rare disease.

CONCLUSIONS

TPE is frequently used in the treatment of neurologic disease. In fact, TPE has been used in an extraordinary number of neurologic diseases (210). However, the effectiveness of TPE has only been shown in a limited number of conditions based on reviews by ASFA, AAN, and Cochrane Library. The diseases with the best data on efficacy and most frequently used include CIDP, GBS, MG both moderate-severe and pre-thymectomy, paraproteinemic polyneuropathies (IgG/IgA), and MS (acute relapses), and LEMS. More trials are needed to understand the role of TPE in the many other neurologic diseases in which it is used. As with any treatment, a careful risk:benefit analysis must be performed for each patient.

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Table I**Overall Conclusions of TPE in Neurology**

Disease	ASFA	AAN	Cochrane
Acute disseminated encephalomyelitis	II	III [*]	
Amyotrophic lateral sclerosis	IV	III [*]	
Chronic inflammatory demyelinating polyradiculoneuropathy	I	I	I
Dermatomyositis or polymyositis	IV	III [*]	
Guillain-Barre´ Syndrome	I	I	I
Inclusion body myositis	IV	III [*]	
Lambert-Eaton myasthenic syndrome	II	III [*]	III
Multiple sclerosis (acute relapses)	II	II	
Multiple sclerosis (CPMS)	III	IV	
Myasthenia gravis (mod-severe)	I	III	II
Myasthenia gravis (pre-thymectomy)	I	III	III
Neuromyelitisoptica	II	III [*]	
Paraneoplastic neurologic syndromes	III	III [*]	
Paraproteinemic polyneuropathies (IgG/IgA)	I	II	III
Paraproteinemic polyneuropathies (IgM)	I	III	
Paraproteinemic polyneuropathies (IgM anti-MAG)			III
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and Sydenham's chorea	I	III	
Phytanic acid storage disease (Refsum's disease)	II	III [*]	
POEMS syndrome	IV	III [*]	
Sydenham chorea		III	
Stiff-person syndrome	IV	III [*]	

I is effective and proven. II is may be effective but evidence not compelling. III is insufficient evidence to conclude. IV is ineffective by evidence.

^{*} not evaluated by AAN as AAN excluded evaluation of conditions for which there was only class IV evidence.

POEMS = Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin syndrome