

# A Double-blind Controlled Pilot Study of Plasma Exchange versus Sham Apheresis in Chronic Progressive Multiple Sclerosis

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**ABSTRACT:** Twenty patients with chronically progressive multiple sclerosis (MS) were randomised in a double-blind controlled study to assess the efficacy of plasma exchange therapy. All patients were immunosuppressed with prednisone and azathioprine and underwent either plasma exchange or sham apheresis. The 10 patients in each group were similar in age, sex, duration of disease and degree of disability. Clinical and laboratory responses were assessed immediately following the course of exchange or sham therapy, and 3 to 6 months later, by individuals blinded to the type of therapy administered. Although modest improvement was suggested on clinical examination in 7 of 10 patients exchanged and 3 of the 10 sham treated group, this was transient and was not accompanied by any change in disability status scores. No differences in abnormal laboratory investigations were demonstrable between the two patient groups following therapy. We conclude that plasma exchange therapy using this protocol is unlikely to be of clinical benefit as an adjunct in the management of chronically progressive M.S.

**RÉSUMÉ:** Une étude pilote à double insu de l'échange plasmatique versus l'aphérèse placebo dans la sclérose en plaques progressive chronique Nous avons étudié 20 patients souffrant de sclérose en plaques progressive chronique dans un protocole à double insu afin d'évaluer l'efficacité de la thérapeutique par échange plasmatique. Tous les patients ont subi une immunosuppression par la prednisone et l'azathioprine en plus de subir soit un échange plasmatique, soit une aphérèse placebo. Les 10 patients de chaque groupe étaient semblables en ce qui concerne l'âge, le sexe, la durée de la maladie et le degré d'atteinte physique. Nous avons évalué les réponses cliniques et de laboratoire immédiatement suivant les traitements et à 3 et 6 mois, cette évaluation étant faite par des individus ignorant le type de thérapie reçue. Il y eut une amélioration modeste à l'examen clinique chez 7 des 10 patients échangés et chez 3 des 10 patients contrôles, mais cette amélioration fut transitoire et ne fut pas accompagnée de modification des scores physiques. Il n'y eut aucune modification biochimique entre les deux groupes de patients suite à la thérapie. Nous concluons donc que l'échange plasmatique a peu de chances de constituer un traitement d'appoint utile cliniquement dans l'approche thérapeutique de la sclérose en plaques chronique.

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The growing evidence for immunopathogenic factors in multiple sclerosis (MS) (Lisak, 1980) has led to recent therapeutic attempts to alter the disease process by immunosuppression and plasma exchange (Tindall et al., 1982; Hauser et al., 1983). Although the precise antigen(s) and type or types of reactions involved in MS are still not clearly understood, preliminary reports (Dau et al., 1980; Weiner and Dawson, 1980) have suggested modest improvement in patients treated with azathioprine, prednisone and plasma exchange. Difficulties in assessing new therapeutic modalities in MS have recently been re-emphasized (McFarlin, 1983). Plasma exchange itself has often been undertaken in only a few cases of a particular disorder

with few randomised controlled trials having been reported at the present time (Shumak and Rock, 1984).

At the MS Research clinic of the University of Alberta, a double-blind pilot study was initiated to assess the effect of plasma exchange therapy in patients with chronically progressive MS, immunosuppressed with prednisone and azathioprine. Patients with a chronically progressive clinical course of MS have continuing disease activity, rarely remit spontaneously and the major causes of disability are readily measurable (McAlpine et al., 1972). The therapeutic aim of the study was to induce modest temporary improvement in major neurological disabilities. In view of the potential placebo effect of this type

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of therapy, a randomised control group underwent sham exchanges in which their separated plasma was re-combined with their cellular constituents and re-infused.

#### PATIENTS AND METHODS

The study was designed as a randomised double-blind trial of true and sham plasma exchange performed by means of a Cobe Centry TPE (Cobe Laboratories, Lakewood, CO) membrane separator, with software tubing specifically designed for sham procedures in study trials made available by Cobe Laboratories. Following initial heparinisation with 1000 u. heparin intravenously, blood was anticoagulated with citrate-phosphate dextrose (Fenwell, Malton) at a ratio of 1 vol CPD to 25 vol blood and processed through the membrane separator. In the true exchange, plasma was removed and discarded, and remaining cellular constituents recombined with 5% albumin (Cutter, Berkeley) with 2 mL 10% calcium gluconate (0.90 meq) (Abbott, Montreal) per 250 ml, and saline to obtain fluid balance.

Twenty volunteer patients between the ages of 23 and 47 years with chronically progressive clinically definite MS (Rose et al., 1976) were admitted following informed patient consent, and approval by the hospital Ethics Review Committee. All patients had progressive disease with continuous decline over at least 2 years before entry into the study. No patient was receiving corticosteroids or other immunosuppressive therapy upon entry into the study, and previous courses of corticosteroids had been unsuccessful in halting the progression of the disease. Patients were excluded if they had serious cardiovascular, renal, hepatic or hematologic disease, and four patients initially admitted to the study were excluded because of problems with vascular access. In-dwelling catheters or arteriovenous shunts were not used in view of the sham arm of the study. It was agreed that if significant benefit was demonstrated with plasma exchange, the sham treated patients would subsequently be offered plasma exchange therapy.

One to one and a half plasma volumes were removed per exchange, performed three times weekly for 2 weeks, and twice in the 3rd week, for a total of 8 exchanges. Each procedure took approximately 1½ hours to complete. In the sham procedure, the patients also underwent 8 procedures lasting approximately 1½ hours each. Patients were unable to distinguish true from sham procedures at the end of the study. Blinding was maintained throughout the study until after the 3-6 month follow-up assessment of the last patient exchanged.

All patients received prednisone and azathioprine begun at the onset of treatment. The dose of prednisone was 30-50 mg every other day, and dose of azathioprine was 150 mg per day in three divided doses. During their stay in hospital, appropriate physiotherapy, occupational therapy, bladder and spasticity management were carried out on all patients. Unsupervised home exercise programs were prescribed upon discharge from hospital.

The physicians (DJC and KGW) responsible for clinical assessment were blinded to the type of exchange procedure. Assessments were made on admission prior to exchanges, immediately following the eight exchanges and again three to six months later. Each assessment was performed at the same time of the day in order to avoid the effects of rest and fatigue. Clinical assessment consisted of neurological examination and a videotape of functional capabilities. Laboratory studies including visual and auditory evoked responses, Goldman visual fields

and urodynamic studies were performed during the pre-exchange and immediate post-exchange assessments but not at the 3-6 month follow-up examination.

Cerebrospinal fluid analyses for total protein, IgG/total protein ratio and myelin basic protein levels were performed prior to and immediately following the exchanges. Student's *t* tests for correlated group means and independent group means was used in the evaluation of the CSF protein values.

Neurological examinations were performed in a semi-quantitative fashion. During each assessment the examiner was blinded to the results of previous evaluations. Visual acuity was recorded. Ocular movement abnormalities in the primary position, during horizontal gaze to the right or left and vertically upward or downwards were graded as normal or as mildly, moderately, or severely impaired. Muscle strength in the upper and lower limbs was graded from 5 (normal) to 0 (complete paralysis). In addition, grip strength and finger to thumb pinch strength were recorded with manometers. The presence or absence of an extensor plantar response was determined. Clonus at the ankles was recorded as absent, unsustained or sustained. Abdominal reflexes were determined to be absent, reduced or normal. Tendon reflexes in the arms and legs were graded as absent, reduced, normal, increased or markedly increased. Vibration sense and proprioception at the distal interphalangeal joint of the index finger and at the metacarpophalangeal joint of the great toes was graded as normal, reduced, severely reduced or absent. Two point discrimination in millimeters was recorded over the palmar surface of the distal phalanx of each index finger. Light touch and pin prick sensations were graded as normal, reduced or severely reduced in the arms and legs. Postural and intention tremors in the arms were recorded as absent or as mild, moderate or severe in intensity. Rapid repetitive index finger to thumb tapping and rapid repetitive hand tapping were recorded as the number of taps per 10 second period (normal >40 per 10 seconds).

Diadochokinesia and the heel-to-shin test were recorded as normal or as mild, moderate or severely impaired. If able to do so each patient had a timed walk, repeated 3 times, over a 24 or a 50 foot distance. Special features of the gait and the need to use assistance devices were noted. In those patients who were able to stand, the heel-to-toe tandem gait was assessed by asking them to take eight steps. It was repeated 3 times and graded as normal or mild, moderate or severely impaired. The major neurological impairments were then summarized and each patient was assigned a Kurtzke disability status score.

Realistic and clinically significant therapeutic objectives were then determined individually. Therapeutic objectives were different for each case. For example, the objective(s) could be to improve strength in the one remaining functional arm in a patient with spastic asymmetrical quadraparesis, to reduce ataxia and tremors in another patient, to improve vision and bladder control in a third, or various combinations in other patients. Unrealistic therapeutic objectives such as producing increased power in totally paralyzed legs were not anticipated. Psychological changes such as improved emotional well being were not studied.

Disabilities with respect to mobility and activities of daily living were videotaped. Depending on the individual patient, activities such as handling of small and large objects, transfers and wheelchair management, gait and stair climbing, mat activities including rolling, bridging and balancing in two and four

point kneeling positions were monitored. The videotapes were rated as stable, worse or improved under the categories of mobility/gait, mat activities and hand functions prior to breaking the randomisation code.

**RESULTS**

The 2 treatment groups were well matched with respect to age, sex, total duration of disease and disability score at entry (Table 1). The Kurtzke disability status scores (Kurtzke, 1955, 1983) pre- and post-plasma exchange or sham exchange, and the clinical response immediately after and 3-6 months following the exchange procedure are seen in Tables 2 and 3. The clinical response for each patient was assessed with reference to the major neurological disability defined at entry, and recorded as either improved, unchanged or worse. Improvement was recorded if performance was better than the pre exchange assessments. Improvement could occur without changing the Kurtzke disability status score by a full point.

One patient in the plasma exchange group showed an improvement in disability score of 1 Kurtzke point following exchange, although neurologic assessment suggested that 7 patients had clinically improved. Clinical assessment 3-6 months later indicated improvement had been maintained in only 2 patients.

Three patients were assessed as clinically improved following the sham procedures, with improvement maintained in 1 patient. One patient treated by sham apheresis deteriorated a full Kurtzke point during the month he was receiving the procedures, and he subsequently died during the following year.

The results of visual and auditory evoked responses, Goldman visual fields and urodynamic studies are expressed in Figure 1. Nine patients in each group were noted to have abnormal visual evoked responses and improvement was recorded in 1 patient in the plasma exchanged group and 3 in the sham group. Three of 9 patients showed improvement in their abnormal auditory evoked responses following plasma exchange, and 1 of 7 abnormal auditory evoked responses improved in the sham group. Only four patients demonstrated abnormal visual fields in the

**Table 1. Clinical Characteristics of True and Sham Exchange Groups**

	Plasma Exchange	Sham Exchange
No. of Patients	10	10
Mean Age (years)	36.7 (28 - 47)	36 (23 - 47)
Sex (M:F)	7:3	7:3
Mean Duration of disease before entry (years)	12.9 (5 - 22)	12.5 (2 - 20)
Mean Kurtzke disability score at entry	6.1 (4 - 7)	6.5 (3 - 8)

**Table 2. Effects of Plasma Exchange Therapy**

Patient No.	Age/Sex	Disease Duration	Major Neurologic Disability	Improvement on Clinical Assessment		Kurtzke Disability Score	
				Post-PE*	3 - 6 months**	Pre-PE	Post-PE
1	28/M	5	ataxia, visual loss	No	No	7	7
2	45/F	22	spastic paraparesis	No	No	5	5
3	47/M	22	spastic paraparesis	Yes	No	7	6
4	32/F	5	gait ataxia, weak left leg	Yes	No	6	6
5	42/M	22	spastic quadraparesis	Yes	Yes	6	6
6	44/M	14	spastic paraparesis, neurogenic bladder	No	No	7	7
7	33/F	12	spastic paraparesis, ataxias and tremors	Yes	No	6	6
8	33/M	10	spastic paraparesis visual loss	Yes	No	7	7
9	31/M	7	spastic paraparesis gait ataxia	Yes	Yes	4	4
10	32/M	10	spastic paraparesis	Yes	No	6	6

\* Immediately following plasma exchange regimen

\*\* 3 to 6 months after plasma exchange regimen

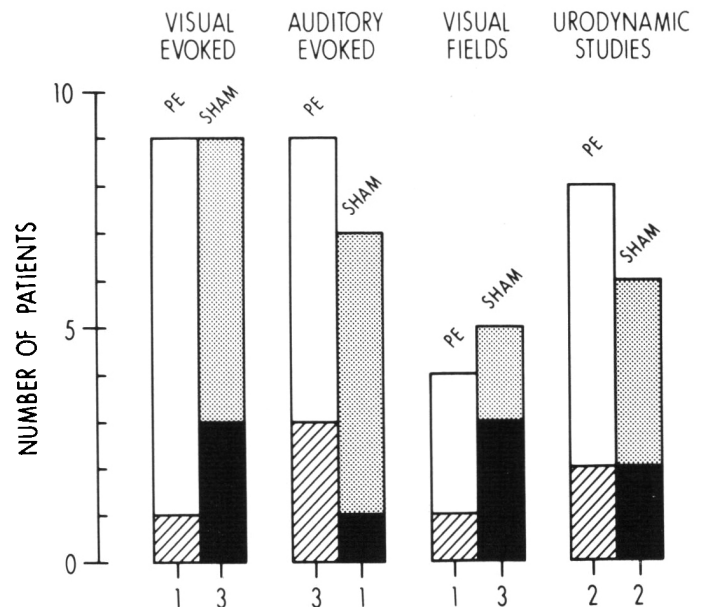


Figure 1 — No. of patients with abnormal studies who improved following either plasma exchange (diagonal lines) or sham exchange (solid black).

**Table 3. Effects of Sham Exchange Therapy**

Patient No.	Age/Sex	Disease Duration	Major Neurologic Disability	Improvement on Clinical Assessment		Kurtzke Disability Score	
				Post-PE*	3 - 6 months**	Pre-PE	Post-PE
1	47/M	16	spastic quadraparesis	No	No	8	8
2	40/F	20	spastic paraparesis, neurogenic bladder	Yes	No	6	6
3	23/F	2	spastic quadraparesis	No	No	8	8
4	27/M	6	gait ataxia & tremors visual loss	No	No	6	7
5	29/M	17	spastic paraparesis ataxias & tremors	No	No	6	6
6	33/M	15	spastic paraparesis ataxias	Yes	Yes	5	5
7	45/M	9	spastic quadraparesis	No	No	8	8
8	38/F	6	gait ataxia	No	No	3	3
9	37/M	17	spastic paraparesis gait ataxia	Yes	No	7	7
10	41/M	17	spastic quadraparesis	No	No	8	8

\* Immediately following sham exchange regimen

\*\* 3-6 months after the sham exchange regimen

plasma exchange group with improvement in one patient, and 3 of 5 abnormal visual fields showed improvement following sham exchange. Similarly, urodynamic studies improved in 2 of the 8 patients with abnormal studies in the plasma exchange group, and in 2 of 6 patients with abnormal urodynamics in the sham treated group. The quantity of improvement in all of these tests was modest, and possibly due to intertest variability. Results of video-assessment are illustrated in Figure 2. Although initial improvement was judged in 4 of 10 patients immediately

following plasma exchange, none was improved at 3-6 months when compared to findings at entry into the study. Of 2 patients in the sham treated group who were judged to have initially improved, only one maintained improvement in gait at 3-6 months.

The differences in C.S.F. total protein, IgG/total protein ratio and myelin basic protein levels before and immediately after either plasma exchange or sham exchange were not statistically significant ( $p > 0.2$ )-Table 4. There was no significant difference ( $p > 0.1$ ) in C.S.F. values obtained in the plasma exchange group compared with the sham treated group.

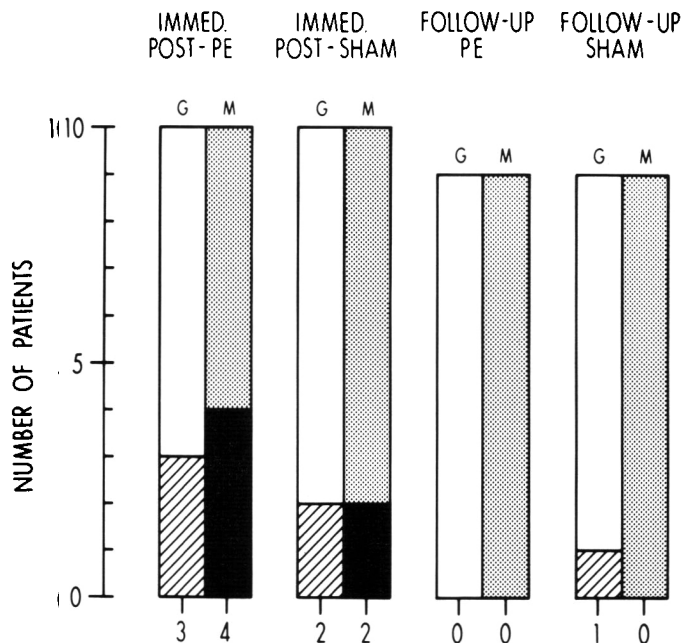


Figure 2 — No. of patients who improved on videoassessment of gait (G, diagonal lines) and mat exercises (M, solid block) immediately following and 3-6 months after either plasma exchange or sham exchange.

**DISCUSSION**

It has been difficult to evaluate the role of therapeutic plasma exchange in diseases such as multiple sclerosis where the pathogenesis and kinetics of antibody production are unclear. The disease may have a variable fluctuating clinical course, concomitant drug therapy is often being given, and no good laboratory marker of disease activity is available. Even where a putative factor can be measurably reduced by plasma exchange, for example reduction in Rh antibody concentration in Rh alloimmunization in pregnancy (Robinson and Tovey, 1980), it is unclear whether this is of significant benefit to the foetus. These difficulties are particularly relevant to multiple sclerosis where symptoms may be accentuated by a variety of factors such as activity, stress, fever, anxiety and depression, and where the placebo effect of therapy is common (McFarlin, 1983). Previous reports of plasma exchange therapy in MS have been uncontrolled (Dau et al., 1980; Weiner and Dawson, 1980; Khatri et al., 1984) or no sham exchange procedure has been included (Tindall et al., 1982; Hauser et al., 1983). This is particularly important when evaluating the potential placebo effect of intensive exchanges using cell-separating equipment in a chronic illness lacking effective therapeutic modalities.

Our results indicate that no clear differences between plasma exchange and sham exchange were demonstrable in this pilot study. Clinical assessment immediately following plasma



**Table 4. Changes in C.S.F. Protein Levels Before and After Exchange**

	Total Protein g/L		IgG/Total Protein Ratio		Myelin Basic Protein µg/L	
	Pre	Post	Pre	Post	Pre	Post
<b>Plasma Exchange</b>						
Mean	0.37	0.36	0.11	0.08	4.8	3.3
Range	0.20-0.58	0.19-0.57	0.06-0.15	0.04-0.14	1.3-11.5	1.0-6.4
±S.D.	0.13	0.12	0.03	0.04	3.0	2.1
n	10	10	10	8	10	10
<b>Sham Exchange</b>						
Mean	0.51	0.45	0.12	0.10	4.1	2.8
Range	0.26-1.19	0.21-1.06	0.06-0.16	0.07-0.14	0.3-8.0	0.9-4.4
±S.D.	0.34	0.28	0.03	0.03	2.9	1.4
n	10	10	9	9	10	10

exchange suggested modest improvement in 7 of 10 patients. This was not supported by significant changes in disability scores and only 4 patients were thought to be improved on video assessment. Improvement was transient, with no improvement recorded on video assessment 3-6 months later. Similar findings were noted in the sham treated group where clinical assessment suggested initial improvement in 3 patients, which was also transient. The two groups of patients were closely matched with respect to abnormal neurological and urodynamic tests, and more sham treated patients appeared to improve compared with the plasma exchange group.

The number and volume of the exchanges was similar to protocols previously used in plasma exchange studies (Dwosh et al., 1983; Hauser et al., 1983) and was greater than the 4-5 exchanges over a 7-10 day period believed to be adequate short-term therapy (Shumak and Rock, 1984). Minor bruising around the ante-cubital venous access sites was common, but no serious side effects were experienced. Four additional patients were withdrawn from the study after one to three exchange procedures due to difficulties with vascular access. Because of the sham procedures in the trial, in-dwelling lines or surgery for arteriovenous shunts with their associated risks of infection were not undertaken.

The immunosuppressive regime was continued for at least 3 months in doses similar to those previously reported (Dau et al., 1980; Howard and Weiner, 1980). Since similar benefit, albeit limited, was demonstrated in both groups of patients, it seems likely that this was due mainly to either placebo effect and physiotherapy, or to immunosuppression, which has previously been reported to produce a favourable response (Ellison and Myers, 1978; Hommes et al., 1980). Any benefit, however, was transient and not demonstrable 3 to 6 months later. Even the benefit obtained with high dose intravenous cyclophosphamide plus ACTH unfortunately does not appear to be maintained beyond 12 months in the majority of patients treated (Hauser et al., 1983).

Our results differ from those of Khatri et al. (1984) who treated 45 MS patients with chronic progressive disease with chronic plasma exchanges, once per week for 10 weeks and then less frequently, together with immunosuppressive therapy using cyclophosphamide (1 to 1.5 mg/Kg of body weight each

day) and prednisone (1 mg/Kg of body weight each alternate day) in a gradually declining dosage. Fourteen of the 45 patients improved by more than 3 steps on the Kurtzke disability status scale and 14 more improved by at least one step. The study was not double-blind or sham controlled. The dramatic improvement observed in over 50% of these patients was not observed in our study using a short course of plasma exchange therapy (8 exchanges during a three week period) combined with daily azathioprine and alternate day prednisone as immunosuppressing agents. Our data supports the conclusions of Tindall et al. (1982) that plasmapheresis 3 or 4 times over a 10 day period followed by a single exchange at monthly intervals for a year combined with daily azathioprine therapy does not appear to produce significant improvement or halt progression of the disease. The study of Tindall et al. (1982) was controlled with a group treated by azathioprine alone. Five of seven patients treated by azathioprine without plasma exchanges progressed when followed for 12 months, and four of seven patients treated by azathioprine with plasma exchanges progressed when followed for the same duration.

We had previously thought (Warren et al., 1982) that C.S.F. myelin basic protein levels might be a useful marker to monitor in MS patients with acute exacerbation receiving this type of treatment. Although there was a tendency for the levels to fall in M.S. patients with chronic progressive disease after both true and sham exchange, this did not reach statistical significance. The C.S.F. IgG levels as a percent of total protein also had a tendency to fall in both the plasma exchanged as well as the sham exchanged groups; but in neither group was the difference statistically significant. The modest falls may have been due to the immunosuppressive therapy administered to both groups of patients. This study also suggests that plasma exchange therapy does not have a reliable beneficial effect on visual or auditory evoked responses, Goldman visual fields or urodynamic studies of bladder function. Modest improvements were noted in a small number of both plasma exchanged and sham exchanged patients and may have been due to intertest variability.

Plasma exchange is expensive and time-consuming. Well-controlled studies are essential in assessing its role, especially in patients who are chronically ill. Sham procedures are particularly important in this clinical setting when evaluating the role

of plasma exchange. Our pilot study, on a limited patient sample, does not support the preliminary favorable responses attributed to plasma exchange in patients with chronically progressive MS.

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