Meta-analysis of clinical studies of the efficacy of plasma exchange in the treatment of chronic progressive multiple sclerosis

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Authors' objectives
To examine the hypothesis that the addition of therapeutic plasma exchange (TPEX) to an immunosuppressive regime increases the regime's efficacy to halt the progression of chronic multiple sclerosis (MS).

Searching
MEDLINE was searched from January 1980 to June 1994 for relevant articles published in English, French and Spanish. The bibliographies of retrieved articles were examined for further studies.

Study selection
Study designs of evaluations included in the review
Clinical trials were included if they were prospective and compared treatment with TPEX to some form of immunosuppression therapy given concurrently. Randomised controlled trials (RCTs) and observational studies were included.

Specific interventions included in the review
TPEX given in doses ranging from 1 to 2 plasma volumes, and at a frequency ranging from 1 to 3 times weekly with one trial reducing the frequency to once per month after the first 10 days. The total number of sessions varied from 4 to 20 and the equipment used provided continuous and intermittent flow.

Immunosuppressive regimes in the treatment and the control groups included oral cyclophosphamide, prednisolone, azathioprine, methyprednisolone and intravenous cyclophosphamide and adrenocorticotropic hormone (ACTH).

Participants included in the review
Patients with a definite diagnosis of MS of the chronic progressive type (CPMS).

Patients with this form of disease were defined as having evidence of continued worsening on serial neurological examinations in the year preceding entry to the trial. Patients could have had either a progressive form from onset, secondary progressive or relapsing progressive disease.

Patients should not have had an acute deterioration prior to trial entry. Studies of TPEX in acute attacks of MS were excluded.

Outcomes assessed in the review
The main outcome measures assessed were changes in: Kurtzke's disability status scale score (DSS), ambulation index, general disability scale and neurological decline, as defined by the investigators.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Studies were assessed according to the use or not of randomisation and blinding of the neurologist assessing the patients. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.
Data extraction
The authors do not state how the data were extracted from the primary studies. However, the difference in the mean change in Kurtzke's DSS scores (mean treatment scores minus mean of comparison group) was calculated separately for each patient group at specified follow-up times.

Methods of synthesis
How were the studies combined?
The following relative odds ratios were calculated: neurological decline, neurological decline by 1 or more grades on the DSS scale, neurological improvement and neurological improvement by 1 or more grades on the DSS scale. Results were calculated at 6, 12, 24 and 36 months of follow-up.

The mean changes in Kurtzke's DSS scores were combined using Cochran's method (see Other Publications of Related Interest no 1). The relative odds of neurological decline or improvement were combined using Peto’s method (see Other Publications of Related Interest no 2).

How were differences between studies investigated?
Homogeneity across the studies was assessed using the Q statistic. The analyses were repeated using only results from RCTs. Sensitivity analyses were performed to investigate a number of factors: the effect of excluding 4 patients whose improvement could have been due to spontaneous recovery from an acute exacerbation of MS, the effect of the blinding of the neurologist assessing the patients, the effect of one control group who had a worse outcome than anticipated and the effect of only considering studies meeting rigorous design criteria.

Results of the review
Six studies in total were included: 4 RCTs (2 double-blind, 1 single-blind, 1 open) and 2 observational studies.

Mean change in Kurtzke's DSS scores measured at 6 and 12 months: 3 RCTs (209 patients) and 1 observational study (20 patients).

Mean change in Kurtzke's DSS scores at 36 months: 1 RCT (112 patients) and 1 observational study (20 patients).

Relative odds of neurological decline in treatment versus the comparison group: at 6-month follow-up, 3 RCTs (209 patients) and 1 observational study (20 patients); at 12-month follow-up 3 RCTs (209 patients) and 2 observational studies (40 patients); at 36-month follow-up, 1 RCT (112 patients) and 1 observational study (20 patients).

Relative odds of neurological improvement: at 6 and 12 months, 3 RCTs (209 patients) and 2 observational studies (40 patients); at 36 months, 1 RCT (112 patients) and 1 observational study (20 patients).

Mean change in Kurtzke's DSS scores at 6 months (treatment minus comparison): all studies, -0.171 (95% confidence interval, CI: -0.377, 0.039; Q statistic, P>0.05).

Randomised studies: -0.177 (95% CI: -0.386, 0.032; Q statistic, P<0.05). Sensitivity analysis after excluding 4 patients: -0.149 (95% CI: -0.359, 0.061; Q statistic, P>0.10).

Mean change in Kurtzke's DSS scores at 12 months: all studies, -0.212 (95% CI: -0.440, 0.017; Q statistic, P>0.05).

Randomised studies: -0.204 (95% CI: -0.437, 0.030; Q statistic, P<0.05). Sensitivity analysis after excluding 4 patients: -0.167 (95% CI: -0.400, 0.065; Q statistic, P>0.10).

Mean change in Kurtzke's DSS scores at 36 months: two studies, -0.104 (95% CI: -0.441, 0.232).

Relative odds of neurological decline in treatment versus comparison group at 6 months: all studies, 0.746 (95% CI: 0.328, 1.696; Q statistic, P>0.25). Randomised studies: 0.879 (95% CI: 0.373, 2.074; Q statistic, P>0.5).

Relative odds of neurological decline in treatment versus comparison group at 12 months: all studies, 0.436 (95% CI:
Relative odds of neurological decline in treatment versus comparison group at 36 months: two studies, 0.520 (95% CI: 0.259, 1.044).

Relative odds of neurological improvement in treatment versus comparison group at 6 months: all studies, 1.981 (95% CI: 1.024, 3.833, P<0.05; Q statistic, P>0.5). Randomised studies: 2.321 (95% CI: 1.116, 4.828, P<0.05; Q statistic, P>0.5).

Relative odds of neurological improvement in treatment versus comparison group at 12 months: all studies, 2.129 (95% CI: 1.032, 4.390, P<0.05; Q statistic, P>0.5). Randomised studies: 2.258 (95% CI: 1.091, 5.860, P<0.05; Q statistic, P>0.5).

Relative odds of neurological improvement in treatment versus comparison group at 36 months: 0.433 (95% CI: 0.102, 1.836).

Authors’ conclusions
There is a need for further clinical research into the possibility of a beneficial effect from TPEX on patients with CPMS likely to experience neurological decline over the ensuing 12 to 24 months.

CRD commentary
This is a thoughtful and clearly-written review with an excellent discussion on the problems of research to date on TPEX therapy. There was an explicit definition of the patient group to be studied and problems encountered in so defining patients were acknowledged. Results of the analysis were clearly-presented and several sensitivity analyses were used to investigate the differences between trials. There was a comprehensive discussion, which illustrated well the problems encountered by reviewers of research in this field.

The following factors were discussed: differences in study design, differences in disease progression, difference in the definition of treatment failure, differences in the statistical power of each study, a failure rate which may vary according to the entry score, the inclusion of patients who are recovering from an acute exacerbation, lack of definition of ‘progressive’, control groups experiencing a worse outcome than that anticipated from investigations into the natural history of multiple sclerosis, impact of multiple comparisons on the validity of conclusions, the possibility of attributing the effect of TPEX to the co-administration of other drugs, and the masking of the TPEX effect by co-interventions used to treat disease progression in the control group.

Very little information is given on the methodologies used in this review. The literature search was limited to one database and this may have resulted in failure to retrieve additional studies. No mention was made of either the cost of TPEX therapy or any adverse reaction resulting from the treatment.

RCTs are combined with observational studies, therefore the results should be treated with caution. The authors’ conclusions are consistent with the results presented.

Bibliographic details

PubMedID
8770707

Other publications of related interest

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Subject indexing assigned by NLM

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**Record Status**
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