Steroids for multiple sclerosis and optic neuritis: a meta-analysis of randomized controlled clinical trials

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Authors' objectives
To assess the effect of steroids on short- and long-term functional improvement and on the prevention of relapses. The treatment duration and dose, and the severity of side-effects, were also evaluated.

Searching
MEDLINE and EMBASE were searched from January 1966 to December 1998 using the following terms: 'multiple sclerosis', 'optic neuritis', 'corticosteroids', 'steroids', 'ACTH' and 'randomised controlled clinical trials' with all subheadings. The reference lists of all the included trials and some reviews were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were included in the review. Both blinded and unblinded trials were eligible.

Specific interventions included in the review
Steroids or adrenocorticosteroid hormone (ACTH). Studies that compared these with any type of control treatment were eligible for inclusion, but trials that compared different doses or modalities of steroid therapy were not considered. The actual therapies in the included studies were prednisone (15 to 70 mg orally, for 14 days to 18 months), methylprednisolone (8 to 1,000 mg orally or intravenously, for 5 days to 18 months) and ACTH (15 to 120 IU intramuscularly or subcutaneously, for 14 days to 18 months).

Participants included in the review
Patients with multiple sclerosis or optic neuritis. Of the studies included in the review, 7 were of mixed multiple sclerosis, 4 were of optic neuritis, 3 were of acute relapses and one was of chronic progression.

Outcomes assessed in the review
The outcome measures that were evaluated were:

lack of improvement by at least one point on the Expanded Disability Status Scale (EDSS) or on the Alexander scale; and

new relapse, defined as the appearance of one or more symptoms that persisted for more than 24 hours, or clinical worsening after a complete remission at the end of the follow-up.

In patients with optic neuritis, complete recovery of visual acuity was considered as a disability improvement of one point on the EDSS, and the occurrence of definite multiple sclerosis during the follow-up was considered equivalent to a new relapse.

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 reviewers performed the selection.

Assessment of study quality
The quality criteria were: concealment of allocation; blindness to treatment allocation; imbalance of primary prognostic variables; withdrawals after randomisation; and incomplete follow-up. Both authors assessed the quality of the trials.
Data extraction
The two authors extracted the data independently, and any discrepancies were resolved by discussion and consensus.

The categories of data extracted were: sample size; diagnosis; intervention; route and dose; length of therapy; length of follow-up; losses to follow-up; and outcomes.

Methods of synthesis
How were the studies combined?
The studies were combined using meta-analytical techniques. There were four main analyses: three on clinical improvement according to time of assessment (within 8 days, 30 days, and 6 to 36 months) and one on relapse prevention. Studies in which patients were evaluated at different intervals were considered in more than one analysis. All patients without improvement in disability and with relapse were considered irrespective of compliance, and whether they were subsequently evaluated at follow-up in order to conduct an 'intention to treat' analysis.

How were differences between studies investigated?
A sensitivity analysis that included only the double-blind randomised controlled trials was conducted. Other subgroup analyses were conducted for the types of clinical course before randomisation, steroid doses and length of treatment. Weighted estimates of the odds ratios (ORs) across studies were calculated for the main and subgroup analyses using the Peto fixed-effect model method. Between-trial heterogeneity was tested for using the chi-squared test. Where heterogeneity was found, the random-effects model was used to calculate the OR.

Results of the review
Twelve studies (n=1,714) were included. The sample sizes of the studies ranged from 23 to 306.

Corticosteroids or ACTH produced a significant improvement in disability or visual acuity at 8 days (OR 0.42, 95% CI: 0.29, 0.63) and 30 days (OR 0.49, 95% CI: 0.37, 0.64), but not on longer follow-up (0.85, 95% CI: 0.67, 1.09). There was some heterogeneity for the studies in the 8-day analysis (chi-squared 17.04, d.f.=7, p<0.02). The treatment did not significantly reduce the number of patients with relapses (OR 0.74, 95% CI: 0.54, 1.01). Both low and high doses were effective for 30-day improvement, but only high-dose and short-term therapy were factors that identified subgroups with some reduction in the risk of new relapse.

Authors' conclusions
Steroid treatment was effective in accelerating short-term recovery in patients with multiple sclerosis or optic neuritis. Whether steroids are also effective in reducing the risk of relapse, and the optimal dose and length of treatment, must still be determined.

CRD commentary
The review addressed an appropriate question using pertinent and well-defined inclusion criteria in terms of the intervention, participants, indication and outcomes. The search strategy included two main electronic databases and no restrictions regarding the date or language appear to have been imposed. A more extensive search might have identified further studies.

The methodology of the review was described adequately in the published article. The selection of the studies was performed appropriately, as was the assessment of the quality of those included. The level of detail of the individual studies presented in the review was adequate but not extensive. The meta-analyses performed were appropriate although the pooling across studies of multiple sclerosis and optic neuritis, as well as across different doses, treatment durations and so on, might be questionable.

Overall, the authors’ conclusions are supported by the findings presented.
Implications of the review for practice and research
Practice: The authors state 'More effective, less expensive, and better tolerated drugs are still needed for the long-term treatment of multiple sclerosis'.

Research: The authors state 'Clinical trials designed to evaluate the long-term effect with steroids alone or in combination with other drugs are still needed'.

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