

Relative efficacy of intravenous methylprednisolone and ACTH in the treatment of acute relapse in MS

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Article abstract—To compare the efficacy of high-dose intravenous methylprednisolone with intramuscular ACTH in the treatment of acute relapse in multiple sclerosis, we undertook a double-blind, randomized, controlled study involving 61 patients. There was a marked improvement in both groups in the course of the study, but no difference between them in either the rate of recovery or the final outcome. High-dose IV methylprednisolone is a safe alternative to ACTH in the management of acute relapse in MS.

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Steroid therapy has become an accepted part of the management of acute relapse in multiple sclerosis (MS), mainly as a result of studies of intramuscular (IM) adrenocorticotrophin (ACTH) suggesting an acceleration in recovery rate.¹⁻³ There have been no comparable studies of oral steroids, and there is no evidence that steroids in any form affect the long-term course of MS.⁴⁻⁶ More recently, pilot studies have indicated that pulse therapy with high-dose intravenous (IV) methylprednisolone may have a striking effect on the recovery rate of acute relapses,⁷⁻⁹ and 2 placebo-controlled trials have supported the value of IV methylprednisolone in relapse.^{10,11} We report a double-blind, randomized, controlled trial comparing the efficacy of IV methylprednisolone with IM ACTH in the management of acute relapse in MS.

Patients and methods. This study, which was carried out between 1983 and 1987, began in a single center (The London Hospital) but was expanded into a multicenter trial in 1986 in order to recruit the required number of patients in acute relapse. Only patients with clinically definite disease¹² entered the study, and recruitment was restricted to patients seen within 4 weeks of the onset of relapse. Relapse was defined as either the onset of new symptoms and signs or a deterioration in existing symptoms and signs of at least 24 hours' duration. Patients were not accepted if they were improving, if they had received steroids in the preceding 6 months, or if their intellectual function was impaired such that they were unable to give informed consent. Other exclusion criteria included the presence of any other neurologic disorder, pregnancy, immuno-

suppressive therapy, severe disability (defined as a pre-relapse score on the Kurtzke disability status scale greater than 5), and any contraindication to steroid therapy, eg, peptic ulcer, psychotic states, severe hypertension, and diabetes mellitus. The study was approved by the Ethical Committees of all the participating hospitals.

Sixty-one patients entered the study; 51 had relapsing-remitting disease, and in 10 patients the acute relapse was superimposed on a chronic progressive course. There were 16 men and 45 women with a mean age of 35 years. The mean duration of disease was 6.9 years, with a mean duration of relapse of 15 days and a mean disability on entry of 4.6 on the Kurtzke disability status scale.

On entry to the study a full history was taken, and each patient underwent a detailed clinical examination. Overall disability was scored using Kurtzke's disability status scale, and Kurtzke's functional scale was used to assess individual disabilities.¹³ Patients were then allocated randomly in a double-blind fashion to receive either IV methylprednisolone (group A) or IM ACTH (group B). Group A received 1 gram methylprednisolone (Solu-medrone, Upjohn) daily for 3 days and simultaneously received IM placebo injections for 14 days. Group B received IV placebo daily for 3 days and at the same time a reducing course of IM ACTH over 14 days, consisting of 80 units for 7 days, 40 units for 4 days, and 20 units for 3 days. The methylprednisolone was dissolved in 100 ml normal saline and was given over 30 minutes. Thus, each patient underwent identical IV and IM regimens.

Patients were hospitalized for a minimum of 7 days and had daily urinalysis and body weight and blood pressure recording. Blood pressure, pulse, and respiratory rate were recorded before, during, and after the IV administration. Patients were assessed clinically and scored on the disability

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Table. Clinical details of trial patients*

	IM ACTH (32)	IV MP† (29)
Male:Female	9:23	7:22
Age (years)	34.9 ± 8.8	35.2 ± 9.3
Age of onset	27.5 ± 7.0	28.7 ± 10.8
Duration of disease	7.3 ± 7.4	6.5 ± 6.0
Disability (Kurtzke)	4.3 ± 1.2	4.6 ± 1.1
Duration of relapse (days)	15.1 ± 7.2	14.9 ± 8.4

* Figures indicate mean ± standard deviation.
† Methylprednisolone.

scales on days 3, 7, 14, 28, and at 3 months after treatment. Blood was taken for full blood count, biochemistry, and glucose on entry and at each clinical assessment. Antispasticity agents were not discontinued and physiotherapy was given when appropriate.

Statistics. The results of the study were assessed using Student's *t* test and the Mann-Whitney rank sum test. The pattern of change in the 2 groups was compared using linear trend analysis. All statistical tests were conducted at the 5% level.

Results. Thirty-two patients received IM ACTH and 29 patients received IV methylprednisolone. There was no significant difference between the 2 groups in sex distribution, age, age of onset, duration, or severity of disease (table). The distribution of lesions associated with the relapse was also similar in the 2 groups. The results were analyzed by a statistician who was unaware of the identity of the treatment groups. They indicated a clear improvement in both groups over the course of the study, but no significant difference between the 2 groups in either rate of recovery or final outcome at 3 months (figure). Mean scores and mean change in scores for each functional system and for overall disability were compared at each assessment for the 2 modes of treatment, using both the Student's *t* test and the nonparametric Mann-Whitney rank sum test. To compare the rate of change over time in the 2 groups, we carried out linear trend analysis of both Kurtzke's functional and disability status scales. No significant difference was found. With our sample size, the power of this test to detect a 1-point difference between the 2 groups was 80%. Finally, in an attempt to produce an analysis that was methodologically unassailable, we coded disability change scores from the pretreatment value as worse, same, or better, and used chi-squared tests to compare the 2 treatment groups. Again, no significant difference was found at any of the follow-up times.

There was no difference between the clinical response of the 10 patients whose relapse was superimposed on a chronic progressive course and that of the remaining 51 patients.

Of the 61 patients, 5 failed to complete the study, 2 on ACTH and 3 on methylprednisolone. The blood sugar of 1 of the patients on methylprednisolone became very high on day 4, and treatment was stopped although assessments continued. A patient on ACTH became

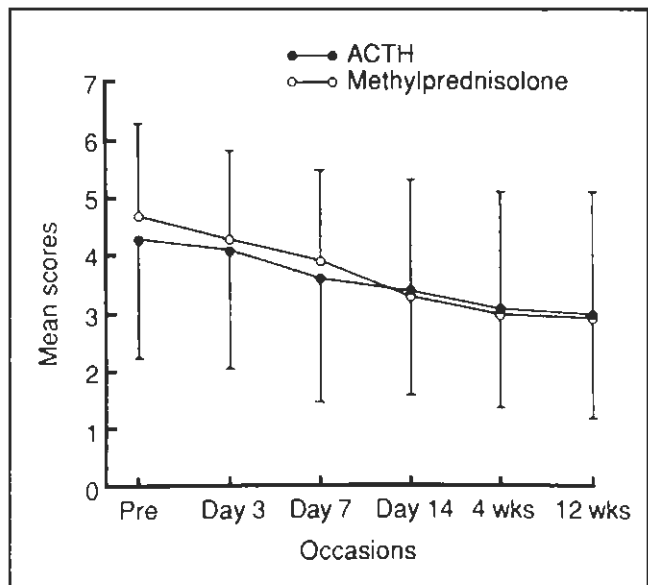


Figure. Comparison of mean Kurtzke disability status scales in patients on ACTH and methylprednisolone over the 12-week course of the study showing the time course of recovery and outcome in the 2 groups of patients. (Bars = 2 standard deviations).

agitated and paranoid on the 13th day and was withdrawn from the study. A 2nd patient on methylprednisolone deteriorated 5 weeks after treatment. She was withdrawn from the study and given oral steroids. Two other patients failed to attend for their 3-month assessment. Subsequent review revealed that there had been no deterioration of their condition. Other side effects included mild ankle edema (3 patients on ACTH), glycosuria (2 patients on ACTH), and a urinary tract infection (patient on ACTH).

Discussion. In this double-blind, randomized, controlled study of MS patients in acute relapse, there was no significant difference in either the rate of recovery or the final outcome between those on a 3-day course of high-dose IV methylprednisolone and those on a 14-day course of IM ACTH. Both groups of patients improved during the study, particularly within the first 14 days. The high doses of IV steroid were well tolerated. Blood pressure did not fluctuate during drug administration, and side effects were less frequent than in the ACTH group. There was no rebound deterioration after the short 3-day course. However, high-dose therapy did not produce the dramatic benefit described in the early uncontrolled studies.⁷⁻⁹

Clinical trials in MS are extremely problematic as a consequence of the relapsing-remitting nature of the disease and its unpredictable course. Thus, any study needs to be as rigidly controlled as possible. Recruitment should be restricted to patients with clinically definite MS, and the study must be double blind.¹⁴ Adequate patient numbers are essential, and groups under comparison should be matched for age and sex, and duration, severity, and pattern of disease. Appropriate statistical analysis should be used, particularly as the disability is usually measured by the nonlinear

Kurtzke scale in which numerically equivalent changes do not carry the same clinical significance at different points on the scale.¹⁵ Many of the studies examining the role of steroids in the management of acute relapse do not satisfy these conditions and suffer particularly from small patient numbers and the inclusion of patients who do not have clinically definite MS. Of the earlier studies, the largest and best organized was the Multi-center Cooperative Study³ which examined the role of ACTH in acute relapse. Among the 197 patients, those on ACTH showed a small but significant improvement in the rate of recovery. As a result of this and earlier studies, steroids were accepted as useful in acute relapse, and, as no comparable study has been carried out on oral steroids, we used IM ACTH in the present study as a comparison to IV methylprednisolone.

Two small, double-blind, placebo-controlled studies^{10,11} suggested benefit from pulse therapy with high-dose methylprednisolone in acute relapse. The larger¹¹ included 22 patients in acute relapse. Thirteen patients received 500 mg IV methylprednisolone daily for 5 days, and these showed a significant increase in the rate of recovery compared with the 9 patients given placebo. Two studies compared high-dose IV methylprednisolone with ACTH in acute relapse.^{16,17} Barnes et al¹⁶ studied 25 patients and showed a significant increase in the rate of recovery, though without effect on final outcome, in those on methylprednisolone. A larger study¹⁷ which involved 60 patients failed to show a significant difference between the 2 treatment regimens.

There has been much speculation as to how steroids exert their limited effect in acute relapse. Possible mechanisms include the resolution of edema, a direct neurophysiologic effect, or an immunologically mediated mechanism. While there is little evidence to suggest a direct effect, immunologic alterations have been attributed to steroid therapy, particularly high-dose methylprednisolone. These include a transient reduction in intrathecal IgG synthesis,^{10,18-20} a decrease in intensity or complete disappearance of CSF IgG oligoclonal bands,^{10,18,19} and a decrease in CSF T lymphocytes.²¹ However, Compston et al²² examined the effect of methylprednisolone on some immunologic factors and found no significant alterations. It is impossible to know if any benefit would be gained from altering these immunologic abnormalities, as their precise role in the pathogenesis of MS remains uncertain. Given the transient and limited effect of steroids in this condition, it is likely that the main, if not the sole, mechanism is the resolution of edema.

In conclusion, this study shows that there is no difference between the effect of high-dose methylprednisolone and ACTH in either the rate of recovery or the final outcome in acute relapse. Giving a 3-day course of IV treatment rather than 14 days of IM injections has obvious advantages in terms of both patient comfort and medical resources. High-dose IV methylprednisolone seems to be a safe, efficient, and acceptable mode of steroid administration.

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