A transcranial magnetic stimulation study evaluating methylprednisolone treatment in multiple sclerosis


Objective – To investigate the efficacy of two different high doses of intravenous methylprednisolone (IVMP) during Multiple Sclerosis (MS) relapses. Background – Transcranial Magnetic Stimulation (TMS) is the most sensitive neurophysiological ascertainment to quantify motor disability, to follow the recovery from an MS relapse, and to detect the response to treatment. Design and method – Twenty-four clinically definite relapsing–remitting MS patients presenting a relapse were randomly assigned to a treatment for 5 days with IVMP 1 or 2 g/day. The response to treatment of each patient was evaluated through Expanded Disability Status Scale (EDSS), Medical Research Council (MRC) score, and TMS by means of motor evoked potential (MEP) parameters. Results – Motor threshold (MT), central motor conduction time (CMCT) and MRC showed a higher improvement with the highest dose of IVMP. Silent period and EDSS improved with both treatments. Conclusion – The dose of 2 g/day of IVMP is more effective in MS relapse.

Many studies provide evidence for the efficacy of high dose intravenous methylprednisolone (IVMP) in the treatment of Multiple Sclerosis (MS) relapses (1, 2).

Oliveri et al. (3), compared two different high doses of IVMP in MS and demonstrated that the higher dosage has a more powerful and prolonged effect in maintaining blood–brain barrier integrity after a clinical relapse. A dosage of 2 g/day of IVMP was significantly more effective than 0.5 g/day in reducing the number of gadolinium-enhancing lesions at Magnetic Resonance Imaging (MRI) 30 and 60 days after the beginning of therapy.

The presence of a parallel dose–effect relationship among IVMP therapy and the recovery from a functional damage of central nervous pathways in MS has not been investigated until now. Evoked potentials are more useful than MRI to detect functional impairment. Among the neurophysiological tests, motor evoked potential (MEP) measures are the most sensitive to follow the recovery from MS relapses, to quantify motor disability, and to detect the response to treatment (4–8).

The aim of the present study is to investigate the efficacy of two different high doses of IVMP during MS relapses using MEP parameters as primary outcome measures of functional damage of central motor pathways.

Materials and methods

Study design and patients selection

Patients with clinically definite relapsing-remitting MS (MSRR) (9), who contacted the local MS centre for a relapse during the period January–October 1999, were consecutively recruited in the study if they were seen within 1 week from the onset of the relapse. For the purposes of the present study, a relapse was defined as the appearance or the worsening of symptoms lasting for at least 24 h and causing an increase of disability of at least 1.0 point at the Expanded Disability Status Scale (EDSS) (10) in the absence of concomitant
fever. A history of epilepsy, head neurosurgery, or the possession of a cardiac pacemaker, were absolute contraindications to Transcranial Magnetic Stimulation (TMS) (11). Patients with diabetes, severe hypertension or peptic ulcers were also excluded. All patients gave prior informed consent.

The study was designed as a double-blind trial. Patients who fulfilled inclusion criteria were assigned to one of two treatment arms using a random number table. The two treatment arms were the following: 1 g/day of IVMP for 5 days (L-Dose group), or 2 g/day for 5 days (H-dose group). To assure blindness, a neurologist (G. Sale) included patients in the study, selected the treatment, and followed the clinical course, two other neurologists (S.C. and D.B.), blind to the treatment, performed the scheduled clinical evaluations, and two neurophysiologists (V.L.B. and A.P.), also blind to the treatment, performed MEPs.

Clinical evaluation
Clinical evaluation was carried out just before (T0) and after 7 (T7) and 21 days (T21) from the beginning of treatment. The disability was quantified by EDSS scoring (10). Motor strength of upper limbs was assessed through the Medical Research Council scale (MRC) with a score comprised between 1 (severe paresis) and 5 (normal strength) (12).

Neurophysiological examination
The same schedule used for clinical evaluation was applied to neurophysiological examination. This was based on TMS. To stimulate the motor cortex a Cadwell MS 10 machine was used. Magnetic stimuli were applied through a figure-of-eight coil placed tangentially over the hand motor cortex of the left and right hemisphere, just over the optimal site for eliciting responses in the contralateral target muscles. Spinal roots were stimulated by placing the coil over C6–C7 spaces and the motor responses were recorded from the same muscles. Electromyograms (EMG) were recorded from the right and left Abductor Pollicis Brevis (APB) muscles using 0.9 cm diameter Ag–AgCl surface electrodes with the active electrode placed over the muscle belly and the reference electrode over the interphalangeal joint. The EMG activity was recorded with a bandpass between 10 Hz and 10 KHz and a display gain ranging from 50 to 200 μV/cm.

The magnetic stimulation threshold for eliciting responses in the relaxed APB muscle, expressed as percentage of maximum stimulator output (MSO), was defined as the intensity of stimulation needed to produce responses of 50 μV in at least 50% of successive trials. Motor threshold (MT) was recorded as 100% if no MEP was elicited with 100% stimulus intensity.

Subjects were given audio-visual feedback of EMG activity to assist in maintaining complete relaxation. Control group consisted of ten healthy volunteers (seven women and three men, mean age 31.8 ± 7.4). The matching was performed following a group-to-group procedure.

All subjects were comfortably seated in a chair and were studied during mild tonic isometric contraction (10–20% maximal effort) of the target muscle using a stimulus intensity of 30% above MT (within the limits of stimulator output). Five responses (MEPs) for each site were collected, averaged and analysed off-line.

We calculated peak-to-peak amplitude of MEP as absolute value and as percentage of the compound motor action potential (CMAP) amplitude obtained with supramaximal electrical stimulation of the median nerve. Cortical and cervical latencies were used to calculate the central motor conduction time (CMCT). We also measured the duration of the transient inhibition of the EMG activity following the MEP evoked during voluntary muscle activity. The silent period (SP) was calculated from the end of the MEP to the reappearance of voluntary activity with amplitude ≥ 20 μV (13). Values ± 2SD above the normal mean were considered as abnormal. Absent values were also considered abnormal, for the analysis they were given the most pathological recorded value. Unpaired Student’s t-test was used to compare patients and controls.

Results obtained at T7 and T21 were expressed as absolute values and as percentage of improvement or worsening compared with the values recorded at the beginning of the study.

Identical stimulation was performed on ten healthy volunteers on three occasions at 7-day intervals. No measurable difference was recorded in the same individuals on the different days. The variation of MEP measures (MT, CMCT and SP) in serially performed studies in normal subjects was ±3%.

Because of the large intertrial variability of this parameter also in controls, as previously reported (14, 15), MEP amplitude was not included in the evaluation of the patients.

Statistical analysis
The overall intragroup analysis was performed using Friedman’s ANOVA. The Wilcoxon’s matched pairs rank sum test was then used to
compare at each time point intragroup differences before and after treatment. The values recorded for each patient at T7 and T21 were compared for intergroup statistical analysis using the Mann–Whitney rank sum test.

The clinical and electrophysiological findings were correlated using Spearman’s rank correlation test. A ‘P’ value of 0.05 was chosen to test statistical significance.

Results
Twenty-four patients with clinically definite MSRR (9) were consecutively enrolled in the study from January to October 1999.

There were nineteen women and five men with age ranging from 18 to 49 years (median 31, mean 32 ± 7.87 years). The mean duration of the disease was 4.1 ± 2.98 years; the mean frequency of relapses was 1.6 ± 0.3/years. Of the original 24 patients, 21 completed the study; two patients (one in H-dose group and one in L-Dose group) dropped out after the first examination, one patient in L-Dose group after the second one. The patients who failed to complete the study did not present major side-effects, but only intolerance to TMS. Of the 21 patients, 12 underwent high dose therapy, nine to low dose therapy. The relapse was monosymptomatic in 10 of the 21 patients (brainstem was affected in five patients, pyramidal system in two patients, sensory system in two patients, and visual function in one). Eleven of the twenty-one patients had an involvement of pyramidal system during their relapse. Statistical analysis was performed considering the mean value calculated from both arms of each patient (type 1 procedure). To disclose some minor differences concealed by such analysis, we considered also the values obtained from each of the 42 arms (type 2 procedure). However, the results obtained with type 2 procedure are to be considered as a trend because of the artificial increase to the sample power.

There was no difference between the two groups with respect to sex, disease duration, mean number of relapses, mean clinical scores (EDSS, MRC) and neurophysiological parameters (MT, CMCT, SP) (Table 1). Mean basal values of neurophysiological parameters were significantly altered in each group of patients compared with controls (Table 2).

Signs of corticospinal impairment were present bilaterally in seven patients, unilaterally in 11; three did not present clinical pyramidal involvement. Before the treatment CMCT was abnormal in 20 of the 42 arms (bilaterally in six, unilaterally in eight patients), MT and SP were altered in 16 (bilaterally in three and unilaterally in 10 patients) and in 22 arms (bilaterally in five patients, unilaterally in 12 patients), respectively. Subclinical MEP abnormalities (one or more abnormal parameters) were present in nine of the seventeen unaffected arms (bilaterally in two patients, unilaterally in five): SP was decreased in six of them, MT and CMCT in five. Three patients had normal MEPs despite of clinical signs of pyramidal tract affection. One patient had absent MEP bilaterally in all follow-up period and so he was not included in the analysis; he was under low-dose treatment. Another patient treated with high dose had absent MEP at T0 and presented a progressive improvement in the follow-up period.

Intragroup analysis
The SP significantly improved in both groups over the follow-up period at the Friedman’s ANOVA

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of patients affected by Multiple Sclerosis according to intravenous methylprednisolone dosage (L-Dose group = 1 g/day; H-dose group = 2 g/day)</th>
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<tr>
<td>L-Dose group</td>
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<tr>
<td>Sex (F/M)</td>
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<td>Age (years: mean ± SD)</td>
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<td>Disease duration (years: mean ± SD)</td>
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<td>No. relapses/year (mean ± SD)</td>
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<td>Basal EDSS (mean ± SD)</td>
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<td>Basal BMRC (mean ± SD)</td>
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Table 2 Neurophysiological parameters of patients (T0) and of controls

<table>
<thead>
<tr>
<th>Controls (n = 10)</th>
<th>L-Dose group (n = 9)</th>
<th>H-dose group (n = 12)</th>
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<tr>
<td></td>
<td>Mean ± SD</td>
<td>P-value</td>
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<tr>
<td>MT (% MSO)</td>
<td>60.0 ± 7.1</td>
<td>67.5 ± 4.1</td>
</tr>
<tr>
<td>CMCT (msec)</td>
<td>8.5 ± 1.1</td>
<td>11.1 ± 3.5</td>
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<tr>
<td>SP (msec)</td>
<td>110.0 ± 12.0</td>
<td>90.0 ± 20.2</td>
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MSO = Maximum stimulator output.
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Figure 1. Neurophysiological and clinical changes during intravenous methylprednisolone therapy (dotted lines: L-Dose therapy; dashed lines: H-dose therapy). When applicable, statistical analyses were performed on the mean value calculated from both arms of each patient. (A) Motor Threshold: (Intragroup analysis, Friedman ANOVA analysis: H-dose therapy $P = 0.06$, L-Dose therapy $P = 0.2$; Intragroup analysis, Wilcoxon’s matched pairs test: H-dose group T0 vs. T7 $P = 0.04$, H-dose group T0 vs T21 $P = 0.05$, L-Dose group T0 vs. T7 $P = 0.09$, L-Dose group T0 vs. T21 $P = 0.08$; Intergroup analysis, Mann–Whitney test: $T7 P = 0.5$, $T21 P = 0.6$); (B) Central Motor Conduction Time: (Intragroup analysis, Friedman ANOVA analysis: H-dose therapy $P = 0.09$, L-Dose therapy $P = 0.2$; Intragroup analysis, Wilcoxon’s matched pairs test: H-dose group T0 vs. T7 $P = 0.5$, H-dose group T0 vs. T21 $P = 0.07$, L-Dose group T0 vs. T7 $P = 0.6$, L-Dose group T0 vs. T21 $P = 0.3$; Intergroup analysis, Mann–Whitney test: $T7 P = 0.5$, $T21 P = 0.5$); (C) Silent Period: (Intragroup analysis, Friedman ANOVA analysis: H-dose therapy $P = 0.001$, L-Dose therapy $P = 0.01$; Intragroup analysis, Wilcoxon’s matched pairs test: H-dose group T0 vs. T7 $P = 0.008$, H-dose group T0 vs. T21 $P = 0.02$, L-Dose group T0 vs. T7 $P = 0.02$, L-Dose group T0 vs. T21 $P = 0.05$; Intergroup analysis, Mann–Whitney test: $T7 P = 0.1$, $T21 P = 0.6$); (D) Expanded Disability Status Scale: (Intragroup analysis, Friedman ANOVA analysis: H-dose therapy $P = 0.0004$, L-Dose therapy $P = 0.0008$; Intragroup analysis, Wilcoxon’s matched pairs test: H-dose group T0 vs. T7 $P = 0.009$, H-dose group T0 vs. T21 $P = 0.01$, L-Dose group T0 vs. T7 $P = 0.02$, L-Dose group T0 vs. T21 $P = 0.008$; Intergroup analysis, Mann–Whitney test: $T7 P = 0.1$, $T21 P = 0.08$); (E) Medical Research Council: (Intragroup analysis, Friedman ANOVA analysis: H-dose therapy $P = 0.1$, L-Dose therapy $P = 0.7$; Intragroup analysis, Wilcoxon’s matched pairs test: H-dose group T0 vs. T7 $P = 0.5$, H-dose group T0 vs. T21 $P = 0.04$, L-Dose group T0 vs. T7 $P = 0.3$, L-Dose group T0 vs. T21 $P = 0.8$; Intergroup analysis, Mann–Whitney test: $T7 P = 0.8$, $T21 P = 0.09$).

Analysis, using either type 1 or type 2 procedure (Fig. 1C). EDSS scores significantly improved in both groups (Fig. 1D). Motor threshold, CMCT, and MRC scale showed a slight improvement that was not significant when type 1 analysis was performed (Fig. 1A, B, E). However, by applying type 2 procedure, we observed a significant improvement over the follow-up period in the highest dose group for MT, CMCT, and MRC scale (Friedman ANOVA analysis: MT: H-dose therapy $P < 0.002$, L-Dose therapy $P < 0.08$; CMCT: H-dose therapy $P < 0.01$, L-Dose therapy $P > 0.05$; MRC: H-dose therapy $P < 0.002$, L-Dose therapy $P > 0.05$).

Wilcoxon’s matched pairs test showed that the improvement of MRC scores in H-dose group reached the significance at T21 (Fig. 1E). The improvement of MT in H-dose group and of SP and EDSS scores in both groups was also significant at T7 and maintained its significance throughout the follow-up period (Fig. 1A, C, D).

Intergroup analysis

At the Mann–Whitney test no significant difference was observed in MT, SP, CMCT values and in MRC and EDSS scores when the two IVMP treatment regimens were compared using type 1 procedure (Fig. 1). However, type 2 procedure suggests a higher improvement of CMCT at T21 ($P < 0.05$), and of muscle strength scores ($P < 0.05$) among patients treated with the high dose regimen.

At T21 we found an inverse correlation between EDSS scores and SP ($r = -0.6; P < 0.0001$) and MRC scores and CMCT ($r = -0.3; P < 0.05$). No correlation was found between clinical scores and neurophysiological parameters before treatment.

Discussion

Several studies on MEP changes have unequivocally shown a good correlation between CMCT and the Kurtzke pyramidal dysfunction scale.
during acute MS relapses (7) or during recovery from attacks (6). The delay of CMCT measurements in MS patients is entirely consistent with the type and the degree of electrophysiological abnormality, i.e. central demyelination which leads to the increase of temporal dispersion or even blockage of signals in the central nervous pathways (16).

Salle et al. (6) provided evidence for the usefulness of MEP as an instrument to assess the effectiveness of short courses of high dose corticosteroid in the treatment of MS relapses. The authors observed a significant improvement of CMCT within 6 days from the initiation of the treatment with 1 g/day of steroids. This suggested that steroids improve central nerve conduction, by restoring transmission of action potentials in pathways damaged by oedema of the myelin sheath. The therapeutic improvement could be the result of the anti-inflammatory and antioedema specific action of steroids (17).

Our study, by comparing two different high doses of methylprednisolone in MS, suggests a greater efficacy of the higher IVMP dose to reverse functional damage of the motor tracts. We used two different statistical approaches to analyse our data. Type 1 procedure is the more appropriate from a statistical point of view. Type 2 procedure is generally used for neurophysiological studies, based on the assumption that each record obtained from each arm has to be considered as a separate event (4, 5, 15); however, it causes an artificial increase of the sample size. It is to be remarked that using type 1 procedure we observed the same greater efficacy of higher IVMP shown by type 2 procedure, whenever not significant.

In contrast with others (6), we did not find any significant improvement of motor conduction with 1 g/day IVMP; the improvement with 2 g/day of IVMP became significant only after the first week. A possible explanation of this difference could take account a different involvement of the corticospinal pathways.

Our results indicate a marked and comparable improvement of EDSS at T7 and throughout the follow-up period in both treatment groups. This low sensitivity of EDSS to differentiate the two groups is in agreement with previous findings (3) and supports the use of a modified EDSS scale (18, 19) or the shift to different rating scales (20). In particular, in our cases the use of scoring systems that takes into account nonpyramidal tract lesions, reduces the correlation between CMCT and EDSS. Differently, MRC score, that is an expression of motor weakness, follows better the improvement of motor conduction, as also evidenced by the negative correlation found between CMCT and MRC scores after treatment.

As well as CMCT, MT and SP have also contributed in detecting upper motor neuronal dysfunction (21–23). It is well known that MT is a measure of cortico-cortical excitability of pyramidal neurons and SP is a useful index of cortical inhibitory activity. We found an increase of MT in 38% of our sample and a decrease of SP in 52% of the examined arms. A comparable pattern of alterations is typical of brain damage involving the primary motor cortex (24, 25). Recently, the increase of MT and the loss of the normal inhibitory cortical activity were the abnormalities most frequently observed in patients with upper motor neuron involvement in motor neuron disease (MND) (23). The authors suggested that the analysis of these parameters increase the sensitivity of TMS in detecting pyramidal dysfunction and to follow disease progression. MT changes we observed in our patients are in agreement with previous studies reporting that the stimulus threshold of MS patients was higher in respect to controls (22). This might be the result of increased temporal dispersion of the descending corticospinal volley in MS patients, which reduces the corticospinal signal on α-motor neurons. Our findings on SP changes are in contrast with that reported in a previous study on MS patients (21). This discrepancy could be because of the patient selection. In fact, the German study selected patients with an uncertain diagnosis of MS at their first clinical manifestations (21), while we included definite MS patients alone. The suggestion that SP modification follows the disease course can be supplied by previous findings on inverse MT changes in MND. In this pathological condition MT lowers at the onset of the disease (26) to increase when the disease progress (23). In our results, MT follows the improvement of CMCT, while SP is the only neurophysiological measure that improves at T7 with both steroid doses. The reason for this pattern of recovery is not immediately clear, but it could be hypothesized as a quicker improvement of neuronal substrates mediating the inhibitory effects of TMS. Further investigations focused on these issues are welcomed.

Considering the frequency of lesions in corticospinal motor pathways in MS and the well-known difficulties in clinically quantifying pyramidal dysfunction, MEPs as MRI are objective and reproducible measures of the disease’s course, providing more sensitive methods to optimize therapeutic trials (27). ‘Very’ high dosage of IVMP may be employed safely and gives a more powerful and sustained therapeutic effect in acute relapses in MSRR patients.
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References
