Quantification of central motor conduction deficits in multiple sclerosis patients before and after treatment of acute exacerbation by methylprednisolone

Andrea M. Humm, Werner J. Z’Graggen, Robert Bühler, Michel R. Magistris, Kai M. Rösler

Departments of Neurology, Universities of Berne and Geneva, Switzerland

Key words: conduction block, relapse, steroid treatment, transcranial magnetic stimulation, triple stimulation technique

Corresponding author:

Prof. K.M. Rösler
Department of Neurology
Inselspital
CH-3010 Bern, Switzerland
Tel. ++41 31 632 30 98
Fax ++41 31 632 30 11
kai-michael.roesler@insel.ch

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ABSTRACT

Objective: To compare the effects of intravenous methylprednisolone (IVMP) in patients with relapsing-remitting (RR-MS), secondary progressive (SP-MS) and primary progressive multiple sclerosis (PP-MS).

Methods: Clinical and neurophysiological follow-up was performed in 24 RR-MS, 8 SP-MS and 9 PP-MS patients receiving 500 mg Solu-Medrol/d during 5 days for exacerbations involving the motor system. We used motor evoked potentials (MEPs) to measure central motor conduction time (CMCT) and applied the triple stimulation technique (TST) to assess conduction deficits. The TST allows an accurate quantification of the number of conducting central motor neurons, expressed by the TST amplitude ratio.

Results: There was a significant increase in TST amplitude ratio in RR-MS (p < 0.001) and SP-MS patients (p < 0.02) at day 5, paralleling an increase in muscle force. TST amplitude ratio and muscle force remained stable at 2 months. In PP-MS, TST amplitude ratio and muscle force did not change. CMCT did not change significantly in any MS group.

Conclusions: In RR-MS and SP-MS patients, IVMP is followed by a prompt increase in conducting central motoneurons paralleled by improvement in muscle force, which most likely reflects partial resolution of central conduction block. The lack of similar clinical and neurophysiological changes in PP-MS patients corroborates previous clinical reports on limited IVMP efficacy in this patient group and points to pathophysiological differences underlying exacerbations in PP-MS.
INTRODUCTION

High dose intravenous methylprednisolone (IVMP) accelerates recovery from acute relapses in multiple sclerosis (MS) \(^1\)\(^{-3}\) and is a standard treatment for acute deteriorations in MS \(^4\). Previous clinical studies suggested that the treatment is less efficient for exacerbations in patients with a progressive course of MS \(^3\)\(^{-5}\), but to our knowledge, no study so far has directly compared the IVMP effects between patients with relapsing-remitting (RR-MS), secondary progressive (SP-MS) and primary progressive MS (PP-MS). IVMP pulse therapy is generally accepted as a safe treatment without major adverse effects \(^6\). However, negative effects of methylprednisolone on neuronal survival have recently been shown in an animal model of progressive MS \(^7\), emphasizing the need for a reevaluation of the current therapy regimen.

Impaired motor performance is a major cause of disability in MS, and therefore transcranial magnetic stimulation (TMS) has been used to evaluate treatment effects. The central motor conduction time (CMCT) is easily obtained by TMS \(^8\)\(^{-9}\), but changes in CMCT do generally not correlate with improved clinical motor deficit after IVMP treatment in MS \(^10\)\(^{-12}\), since slowing of conduction is not, or only marginally related to clinical function \(^9\)\(^{13-15}\).

Motor function relates to the number of conducting central motor neurons, which in theory, should be reflected by the size of the TMS response. In practice, however, MEP size parameters (amplitudes and areas) are not sensitive to quantify conduction deficits. Two factors obscure the relation between MEP size and number of conducting central motor neurons, namely (i) desynchronization of the TMS induced motor neuron discharges causing variable degrees of phase cancellation, and (ii) repetitive discharges of spinal motor neurons in response to TMS \(^16\). Both factors affect MEP size considerably, unpredictably, and vary between subjects and from one stimulus to the next \(^16\)\(^{17}\). The triple stimulation technique (TST) eliminates the effects of discharge desynchronization and repetitive discharges on TMS responses, such that an accurate quantification of the proportion of conducting central motor neurons is possible \(^16\). Use of the TST increased the sensitivity to detect a central motor conduction deficit in MS by a factor of 2.86, and the TST response size correlated with the clinical motor deficit of the patients \(^18\). Moreover, the TST allowed detection of transient small changes of conduction deficits in MS patients related to changing body temperature ("Uhthoff phenomenon"), which correlated well with walking velocity \(^19\).

In the present study, MS patients receiving IVMP for an acute exacerbation involving the motor system were followed clinically and neurophysiologically with the TST. All patients were examined just prior to the start and at the end of 5 days IVMP; in some of the patients a
second follow-up investigation took place 2 months after the start of IVMP. Our results point to considerable differences of treatment efficacy between patients with different disease courses.

METHODS

Patients
The study was approved by the local ethics committee. All patients gave written informed consent.

Forty-one patients with definite MS were enrolled in the study: 24 patients with relapsing-remitting MS (RR-MS), 8 with secondary progressive (SP-MS) and 9 with primary progressive (PP-MS) MS. Disease duration was defined as the time elapsed between the first disease manifestation (determined clinically or by history taking) and the current investigation. All patients suffered from a relapse with clinical involvement of the corticospinal tract to the lower limbs (i.e., hyperreflexia, extensor plantar response, spasticity and/or paresis). A relapse was defined as a newly observed neurological deficit without evidence of spontaneous improvement for at least 24 hours. In all cases, the decision of whether a Methylprednisolone treatment was started or not was taken by clinical neurologists not involved in the study. In the 17 included patients with chronic MS, the disease course was not always known at the start of the treatment and a worsening of symptoms or new symptoms was suspected, so that a treatment was started. In our department, a methylprednisolone treatment is often given in ambiguous clinical situations, because of the low risk of short term adverse effects. Clinical and electrophysiological examinations were performed just before starting methylprednisolone treatment (= day 0; Solu-Medrol 500 mg/d intravenously for 5 consecutive days followed by oral prednisone tapering over 10 days) and at the time of the last methylprednisolone infusion (= day 5). Twenty-eight patients were available for a third investigation 67.6±10.8 days after study begin (= 2 months).

To assess disease-independent effects of IVMP on pyramidal tract function, clinical and electrophysiological examinations were performed on days 0 and 5 as described above in 4 patients presenting with an isolated optic neuritis. Extensive diagnostic work-up (clinical examination, analysis of cerebrospinal fluid, somatosensory and motor evoked potentials, brain MRI) found no evidence of MS in these patients. They were assigned to identical IVMP treatment as the MS patients.
Clinical assessment
At the beginning of the study, the EDSS 21 was calculated for all MS patients. Muscle force of the distal lower limbs (i.e., extension and flexion of foot and toes) was graded according to the British Medical Research Council scale (BMRC grade 1-5; grade 1 reflecting severe paresis and grade 5 full muscle strength) and presence or absence of pyramidal signs (i.e., hyperreflexia, extensor plantar response and/or spasticity) was noted. In MS patients, the clinically most affected leg was chosen for electrophysiological testing; in patients with isolated optic neuritis one leg was chosen randomly. The same examiner reassessed muscle force and pyramidal signs before neurophysiological testing on day 5 and after 2 months.

Electrophysiological methods
A Viking Select apparatus (Nicolet, Madison, Wisconsin, USA) was used for the recordings. Bandpass filters were 2 Hz – 10kHz. Recordings were taken from the abductor hallucis muscle (AH) using silver electrodes (diameter 0.8 cm) in a belly-tendon montage.

For TMS, a Magstim 200 stimulator (maximal output 2.0 T) was used with a double cone (110 mm) hand-held coil (Magstim Company, Spring Gardens, Whitland, Dyfed, UK). The coil was placed over the vertex in anterior-posterior current orientation. Small coil displacements were made in all directions until the position yielding the largest response was found. This position was then maintained throughout the examination. Magnetic stimuli were applied while the patient contracted the target muscle slightly. The MEP latency was defined as the shortest latency out of 6-8 trials. The CMCT was calculated using the following formula:

\[ \text{CMCT} = \frac{\text{MEP latency} - (\text{F-wave latency + CMAP}_{\text{ankle}} \text{ latency}-1)/2}{2^{23}}. \]

The TST to the lower limbs was described previously in detail 24 (see Fig. 1 for a summary of the principle). In short, TMS was combined with supramaximal stimuli of the tibial nerve at the ankle and the sciatic nerve at the gluteal fold 24. The peripheral stimuli were given using the two stimulators of the Viking EMG machine. The TST was achieved by using a dedicated software package for the Nicolet Viking apparatus provided by Judex AS (Aalborg, DK). The delays between the three stimuli were calculated as follows:

- Delay I (brain-ankle) = minimal MEP latency – CMAP_{ankle} latency
- Delay II (gluteal-ankle) = CMAP_{gluteal} latency – CMAP_{ankle} latency

The TST_{test} curve was then compared to the TST_{control} curve, obtained by replacing the TMS by a maximal electrical stimulus to the sciatic nerve at the gluteal fold with appropriate delays (delay I = delay II = CMAP_{gluteal} latency - CMAP_{ankle} latency) 24.
Statistics
The TST amplitude was expressed as the amplitude ratio of $\frac{\text{TST}_{\text{test}}}{\text{TST}_{\text{control}}}$ (termed TST amplitude ratio). To test differences between group means, non-parametric tests were applied (Kruskal Wallis test for multiple unpaired groups, Mann Whitney U for unpaired two group comparisons, Wilcoxon signed rank test for paired two-group comparisons). The null hypothesis was rejected at the 0.05 level of significance.

RESULTS
Baseline measurements (day 0)
Clinical and electrophysiological characteristics of the patients are summarized in table 1. MS groups differed significantly for age ($p = 0.005$) and disease duration ($p = 0.001$). Most patients were treated and investigated within 2 months of the first possible symptom of the current relapse. In some patients, treatment was started later, caused by differential referral patterns to our centre (see ranges in table 1). It is noteworthy however that nonparametric testing revealed no significant difference in relapse duration before treatment between the patient groups ($p = 0.2$). At the time of the investigation, only one SP-MS patient was under simultaneous immune-modulatory treatment (beta interferon).

The mean EDSS score was higher for SP-MS than RR-MS patients ($p = 0.001$), whereas it did not differ significantly between P-MS and RR-MS ($p = 0.18$) and between P-MS and SP-MS ($p = 0.09$). Weakness of the target limb was generally mild to moderate ($\geq$ grade M4) and did not differ significantly between the MS groups ($p = 0.2$). Apart from impaired vision, the clinical examination was normal in isolated optic neuritis patients.

The mean TST amplitude ratio was reduced in all MS groups, but normal in patients with isolated optic neuritis (lower normal limit = 88.4% 24). Detailed results are provided in table 1. The reduction of TST amplitude ratio did not differ significantly between MS groups ($p = 0.3$). The mean CMCT was slightly prolonged in RR-MS (upper normal limit = 15.1 ms 24), and markedly prolonged in SP-MS and PP-MS ($p < 0.01$ compared to RR-MS). CMCT was within normal limits in all isolated optic neuritis patients.
Table 1: Clinical and electrophysiological characteristics at day 0. Given are medians (range)

<table>
<thead>
<tr>
<th>Disease course</th>
<th>RR-MS</th>
<th>SP-MS</th>
<th>PP-MS</th>
<th>ION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>24</td>
<td>8</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Gender (female: male)</td>
<td>11:13</td>
<td>5:3</td>
<td>5:4</td>
<td>1:3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36 (23-54)</td>
<td>48 (32-59)</td>
<td>54 (32-59)</td>
<td>46 (43-50)</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>8.5 (0.3-240)</td>
<td>74 (15-384)</td>
<td>12 (12-84)</td>
<td>-</td>
</tr>
<tr>
<td>Duration of relapse (months)</td>
<td>1 (0.3-7)</td>
<td>2.4 (0.3-4.5)</td>
<td>4 (0.3-7)</td>
<td>0.8 (0.3-1)</td>
</tr>
<tr>
<td>EDSS</td>
<td>3 (1.5-4)</td>
<td>4 (2.5-6)</td>
<td>3 (2.5-6)</td>
<td>-</td>
</tr>
<tr>
<td>Paresis (BMC grade)</td>
<td>5 (3-5)</td>
<td>4 (3-5)</td>
<td>4 (3-5)</td>
<td>5 (5-5)</td>
</tr>
<tr>
<td>TST amplitude ratio (%)</td>
<td>68.8 (7.8-98.6)</td>
<td>33.5 (15.9-84.4)</td>
<td>52.6 (3.6-86.7)</td>
<td>95.5 (91.9-100)</td>
</tr>
<tr>
<td>CMCT (ms)</td>
<td>15.6 (7.2-30.4)</td>
<td>20.8 (17.6-28.1)</td>
<td>21.8 (16.5-32.8)</td>
<td>12.5 (11.2-14.5)</td>
</tr>
</tbody>
</table>

* p < 0.01 for comparison of MS patients (Kruskal Wallis); ** ION: isolated optic neuritis

Short-term follow-up (day 0 vs day 5)

Methylprednisolone was well tolerated except by one PP-MS patient who experienced transient arterial hypertension. Muscle force increased significantly in RR-MS patients (mean force on day 0: 4.7±0.5; day 5: 4.9±0.2; p < 0.02). In SP-MS patients, there was a similar tendency (p = 0.07), whereas no conspicuous change in muscle force could be detected in PP-MS (p = 0.4). In most MS patients, pyramidal signs were less pronounced, but statistical analysis could not be performed since quantification of small changes in pyramidal signs is problematic. All optic neuritis patients had normal muscle force and absence of pyramidal signs.

The mean TST amplitude ratio increased significantly in RR-MS (p = 0.0005) and SP-MS patients (p = 0.017), but remained unchanged in PP-MS and isolated optic neuritis patients (p > 0.05; Fig. 3A; patient examples in Fig. 2). TST amplitudes increased in most in patients with a favourable clinical response to IVMP, while they were barely changed in patients not clinically responding to the treatment. CMCT remained unchanged in all patient groups (p > 0.05; Fig. 3B).
Long-term follow-up (day 5 vs 2 months)
Eighteen RR-MS patients, 7 SP-MS patients and 3 PP-MS patients without further clinical relapses were available at two months for the third investigation. Five RR-MS and 2 SP-MS patients had started immune-modulatory treatment in the meantime (6 beta interferon, 1 glatirameracetate). No statistically significant changes of muscle force and electrophysiological parameters where found compared to day 5 (Fig. 3); and the clinical examination remained basically unchanged.

DISCUSSION
We performed a clinical and neurophysiological follow-up in RR-MS, SP-MS and PP-MS patients receiving IVMP for an acute exacerbation involving the motor system. The principal findings were: i) in RR-MS and SP-MS patients, a significant increase of the number of conducting central motor neurons (reflected by an increased TST amplitude ratio) was found after 5 days of treatment, paralleling an increase of muscle force. At the 2 months follow-up, there was no further significant improvement or deterioration, with a stabilisation of TST amplitude ratio and muscle force. ii) In PP-MS patients, the treatment caused no significant changes of TST amplitude ratio and muscle force. iii) CMCT did not change significantly in any MS patient group.

An untreated control patient group was not included in our study, because we judged unethical to exclude patients from a treatment considered as a standard therapeutic approach 4. Nonetheless it is likely that – averaged across patients - the observed changes were related to the IVMP treatment. In all of our patients, worsening of symptoms occurred until the beginning of the treatment. Progression stopped or symptoms regressed notably during the five days of IVMP treatment. The close chronological relation between the treatment and the amelioration suggests that the observed clinical and electrophysiological changes represented an effect of the treatment and not just the natural course of the disease. For an estimation of possible disease-independent effects of IVMP on central motor conduction, we analysed 4 patients with isolated optic neuritis receiving an identical IVMP regimen as the MS patients. In these patients, whose central motor conduction was unaffected, we observed neither clinical nor neurophysiological changes after IVMP treatment. Likewise, TST amplitude ratio did normally not change in MS patients not improving clinically from the IVMP treatment (“non-responders”).
The increase of TST amplitude ratio during the IVMP treatment observed in our RR-MS and SP-MS patients is best explained by the reduction of a central motor conduction block.
Conduction block is an important cause of conduction failure and clinical deficit in acute demyelination\textsuperscript{15-25}. It can result from segmental demyelination (which would not immediately respond to steroid treatment), but may also be the consequence of oedema and of inflammatory cytokines\textsuperscript{15-26}. IVMP has marked anti-oedematous, anti-inflammatory, as well as membrane stabilizing properties\textsuperscript{4-27}. The rapidly occurring reduction of conduction deficit in our RR-MS and SP-MS patients could thus readily be explained. Theoretically, an increase of TST amplitude ratio could also be related to an increase of cortical excitability. However, changes in cortical excitability were previously not found after methylprednisolone treatment of acute relapses (dosage: 1 g/day for 5 days), using the resting motor threshold as a measure of excitability\textsuperscript{10}. In the present study, resting motor threshold was only determined in a small number of patients, where it remained unchanged (results not shown). Taken together, it is unlikely that changes of cortical excitability explain the present results.

Several factors may account for the lack of electro-clinical improvement in the PP-MS patient group. First, from histo-pathological\textsuperscript{28} and MRI studies\textsuperscript{29-31}, there is increasing evidence that acute inflammation is less prominent in this group of MS patients, resulting in limited efficacy of IVMP. Second, axonal loss might be more substantial in PP-MS than in SP-MS and RR-MS\textsuperscript{32} and conduction deficits caused by axonal loss are not likely to change rapidly in response to IVMP, or to any other treatments. The TST quantifies the number of conducting axons, but a reduction of TST amplitude does not differentiate between loss of axons and conduction block\textsuperscript{18}. The lack of improvement in follow-up investigations is well in line with axonal loss having taken place, although persistent conduction block cannot be excluded. Our finding of reduced efficacy of IVMP in PP-MS corresponds well with previous clinical observations of less frequent and less pronounced IVMP effects in progressive patients\textsuperscript{3-5}. Nevertheless, the present data do not rule out beneficial effects of IVMP, because further deterioration could have occurred in untreated patients\textsuperscript{5}, and because the possibility of dose-dependent effects in high dose regimens\textsuperscript{10} were not investigated.

So far, only a few studies used MEPs for objective assessment of the IVMP effects in MS patients\textsuperscript{10-12}. None of these studies analysed MEP amplitudes, because the size of conventional MEPs is inaccurate to measure conduction deficits. Use of the TST circumvents this problem, and is able to demonstrate IVMP associated changes in central motor conduction deficits. It shows considerable differences of treatment efficacy between patients with different disease courses.

Given the lack of reliable MEP amplitude measurements, previous studies concentrated mainly on measuring the CMCT, and several authors reported CMCT reductions after IVMP
treatment. While these studies generally found an association between overall disease severity and CMCT, a relationship between the change of the clinical motor deficit of the investigated limb and of the corresponding CMCT could not be demonstrated in any of these studies. In the present study, CMCT did not change significantly in any MS patient group, emphasizing the lack of sensitivity of this measure, and of a relation between CMCT and conduction deficit. We have previously observed that prolongations of CMCT relate to diseases course (relapsing-remitting vs. chronic progressive MS) but not to the motor deficit of a given patient.

Our results suggest a limited efficacy of IVMP for acute exacerbations in PP-MS patients. These findings are of special clinical interest, since methylprednisolone may induce neuronal apoptosis in progressive MS. In order to critically reevaluate the role of IVMP in PP-MS exacerbations, further studies combining clinical and neurophysiological assessment in a larger number of PP-MS patients would be needed. It also remains to be determined whether the efficacy of IVMP in these patients depends on the degree of the acute deterioration in pyramidal tract function and whether there is a dose-dependent effect of IVMP.

ACKNOWLEDGEMENTS

A.M.H. is supported by a Swiss national grant for a fellowship in clinical neurophysiology (Grant 31-226). Additionally, this study was supported by the Swiss National Science Foundation (Grants 3100-053748.98/1 and 3200B0-100701).
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FIGURE LEGENDS

Fig. 1. Triple stimulation technique (TST) principle for recordings from lower limbs. The motor tract is simplified to 3 spinal motor neurons; horizontal lines represent 3 motor units of the abductor hallucis muscle. Black arrows depict action potentials that cause a trace deflection, open arrows those that do not. Below, the trace recording is given at each time point. A: In TST test; (A1) a submaximal transcranial stimulus excites 2 spinal motor neurons out of 3 (large open arrows). (A2) On 2/3 neurons, TMS induced action potentials descend. Desynchronization of the 2 action potentials has occurred (possibly at spinal cell level). After a delay, a maximal stimulus is applied to the tibial nerve at the ankle. It gives rise to a first negative deflection of the recording trace. The antidromic action potentials collide with the descending action potentials on motor neurons 1 and 2. The action potential on neuron 3 continues to ascend. (A3) After a second delay a maximal stimulus is applied to the sciatic nerve at the gluteal fold. On motor neuron 3, the descending action potential collides with the ascending action potential. On neurons 1 and 2, no collision occurs, and action potentials continue to descend on both neurons. During their descent, only a minor degree of desynchronization occurs as typical for peripheral nerves. (A4) Action potentials on motor neurons 1 and 2 evoke a well synchronized muscle response, giving raise to the second negative deflection in the recording trace. Note that motor neurons 1 and 2 were those initially excited by TMS. B: In TST control; (B1) a maximal stimulus is applied to the sciatic nerve at the gluteal fold. (B2) After a delay, a maximal stimulus applied to the tibial nerve at the ankle is recorded as the first deflection of the TST control trace. (B3) After a delay a maximal stimulus is applied to the sciatic nerve, evoking action potentials on all neurons. During their descent, a minor degree of peripheral desynchronization occurs, matching (and calibrating) the desynchronization that occurred during the TST test procedure. (B4) A well synchronized response from the 3 motor neurons is recorded as the second deflection of the TST control trace. The test response is quantified as the ratio of TST test : TST control curves.

Fig. 2. TST recordings of a patient with RR-MS (A) and with P-MS (B), the upper row showing the recordings at day 0, the lower row at day 5. For all recordings, superimposition of the best TST_{test}, the TST_{control} curve and a baseline (obtained by supramaximal stimulation of the tibial nerve at the ankle) was performed. The sweep of the traces is delayed and starts with the second stimulus of the TST (electrical stimulation at the ankle). The TST amplitude ratio, calculated by TST_{test} / TST_{control}, is given for each recording. In the RR-MS patient, there is a clear increase in TST amplitude ratio at day 5 resulting in normalization of the TST-AR,
whereas the TST amplitude ratio remains reduced and virtually unchanged in the PP-MS patient. The CMCT, obtained by conventional MEPs (not shown), was normal in RR-MS (day 0 = 13.9 ms, day 5 = 13.5 ms), but prolonged in PP-MS (day 0 = 19.2 ms, day 5 = 16.8 ms). Overall the changes in CMCT did not reach significance in any MS group, although there was a clear decrease of CMCT in some patients as shown here for PP-MS. Note that the distance between the two negative deflections of the TST recording does not directly reflect CMCT, but depends on the individually calculated delay I and II.

Fig. 3. Mean TST amplitude ratio (A) and mean CMCT (B) are shown separately for the different patient groups before (day 0) and after IVMP (day 5 and 2 months). ION summarizes patients with isolated optic neuritis. Error bars represent SEM. The dashed line indicates the lower normal limit (LNL = 88.4%) for the TST amplitude ratio and the upper normal limit (UNL = 15.1 ms) for the CMCT respectively. Significant changes after IVMP are indicated by brackets and the appropriate p-value (Wilcoxon signed rank test) on the top of the diagram. For RR-MS and SP-MS a significant increase in TST amplitude was found from days 0 to 5. From day 5 to the 2 months follow-up, a small, but not significant increase of TST amplitude ratio occurred in RR-MS and SP-MS patients (number of available patients indicated in the headline of the diagram); the number of available PP-MS patients at 2 months was too small for statistical analysis. There was no significant change in CMCT for any patient group at any time point. Note that the mean CMCT of SP-MS and PP-MS was always significantly prolonged compared to RR-MS (indicated by *).
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J Neurol Neurosurg Psychiatry published online September 20, 2005

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