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# Treatment of spasticity with repetitive magnetic stimulation; a double-blind placebo-controlled study

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*The effect of repetitive magnetic stimulation on spasticity was evaluated in 38 patients with multiple sclerosis in a double-blind placebo-controlled study. One group was treated with repetitive magnetic stimulation (n=21) and the other group with sham stimulation (n=17). Both groups were treated twice daily for 7 consecutive days. Primary end-points of the study were changes in the patients self-score, in clinical spasticity score, and in the stretch reflex threshold. The self-score of ease of daily day activities improved by 22% (P=0.007) after treatment and by 29% (P=0.004) after sham stimulation. The clinical spasticity score improved $-3.3 \pm 4.7$ arbitrary unit (AU) in treated patients and $0.7 \pm 2.5$ AU in sham stimulation (P=0.003). The stretch reflex threshold increased $4.3 \pm 7.5$ deg/s in treated patients and $-3.8 \pm 9.7$ deg/s in sham stimulation (P=0.001). The data presented in this study supports the idea that repetitive magnetic stimulation has an antispastic effect in multiple sclerosis. Future studies should clarify the optimal treatment regimen.*

**Keywords:** *repetitive magnetic stimulation; multiple sclerosis; spasticity; treatment; stretch reflex*

## Introduction

Spasticity in patients with multiple sclerosis (MS) is primarily treated pharmacologically. Baclofen, diazepam, and tizanidine are all superior to placebo in reduction of spasticity as shown in double-blind-crossover trials.[1,2] Side-effects, however, are common including drowsiness, dizziness, nausea and muscle weakness and in several patients the medication is stopped either because of the side-effects or because of insufficient effect. Non-pharmacological treatment techniques have been developed as a supplement in the treatment of spasticity. Electric stimulation of neurons of the spinal cord by epidural implanted electrodes was introduced in the treatment of spasticity by Cook and Weinstein in 1973, but the effectiveness remains uncertain.[3,4] Non-invasive transcutaneous electrical stimulation of peripheral nerves has also been attempted. Levin and Hui-Chan reported an effect of 3 weeks electrical nerve stimulation of the peroneal nerve on spasticity in thirteen patients with spastic hemiparesis.[5] Clinical spasticity improved by 16% and the stretch reflex threshold increased by 35%.

Neurons can be excited by a rapid, time-varying magnetic field which induces an electrical field in the tissue. The penetration of the magnetic field is independent of the density and resistance of the tissues and is effective enough to pass the cranium and the spine and excite nervous tissue. For clinical use magnetic stimulation was introduced in 1982 by Polson *et al* who stimulated peripheral nerves by using a single pulse of magnetic field and in 1985 Barker *et al* stimulated neurons of the motor cc tex.[6,7] The technique of magnetic stimulation is now well-established in clinical neurophysiology and applied in studies of motor pathways. To use repetitive magnetic stimulation in treatment of spasticity is a new approach. In a previous uncontrolled preliminary report repetitive magnetic stimulation appeared effective in treatment of spasticity in MS patients.[8] As a consequence the present double-blind placebo-controlled study was conducted.

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## Patients and methods

The study included 38 patients with multiple sclerosis (MS), 26 females and 12 males with a median age of 44(26–67) years and an EDSS score below 7.0. Inclusion criteria were (1) clinical definite or laboratory supported definite MS according to criteria by Poser *et al*; (2) a stable neurological condition for at least 6 months; (3) severity of lower limb spasticity $\geqslant 2$ according to Ashworth score over at least one joint and (4) preserved walking performance for 10 m.[9,10] Exclusion criteria were epilepsy, other neurological disorders, pregnancy and implanted spinal metal, drug infusion pump and pacemakers. In addition, patients who had been exposed to magnetic stimulation previously were excluded. Antispastic medication with baclofen, tizanidin, and diazepam as well as functional electric peroneal nerve stimulation was discontinued one week before the study. Two patients used drop foot stimulation to improve walking and thus the tibial muscle was stimulated during walking. This was continued during the whole study period. All patients were encouraged to sustain the usual daily physical activity and physical therapy throughout the experiment.

Patients were randomly allocated to a double-blind placebo-controlled study (Table 1). One group was treated with repetitive magnetic stimulation ($n$=21) and the other group with sham stimulation ($n$=17)

Table 1 Characteristics of the spastic multiple sclerosis patients

| | Number | Sex | Age (year) | MS duration (year) |
|---|---|---|---|---|
| Placebo group | 17 | 5 M, 12 F | 44 (26–66) | 13 (2–30) |
| Treatment group | 21 | 7 M, 14 F | 44 (34–67) | 12 (2–34) |

twice daily for 7 consecutive days. Following a baseline score (Test I) at the day before treatment start the effect was evaluated one day (Test II), 8 days (Test III), and 16 days (Test IV) after the last stimulation. Repetitive magnetic stimulation was given by a magnetic stimulator with an oil-cooled coil constructed in our laboratory.[11] The coil has an outer winding diameter of 13.4 cm consisting of a 16-turns copper tube. The stimulus has a biphasic waveform with a pulse width of 240 μsec, a rise time of 60 μsec, and a maximum magnetic field of 1.2 Tesla. To exclude any stimulation of lumbal and sacral nerve roots the coil was placed in the midline of the back at mid-thoracic level with the caudal part of the coil at the eighth thoracic vertebra. The subjects were stimulated in a relaxed supine position for 25 min with repeated periods of stimulation for 8 s at 25 Hz followed by 22 s of repose and the magnetic field strength was gradually increased to 0.7 Tesla within a few minutes. One patient tolerated only a maximum field strength of 0.6 Tesla. The sham stimulation paradigm was identical with the active stimulation paradigm except: (1) A 15-cm plastic tube was inserted between the stimulation coil and the body surface; (2) To conceal the placebo procedure from the patient three active single stimulations at 5 s intervals were given before the tube was inserted. The contact plate was physically identical with the surface of the magnetic coil. The small mechanical displacements of the coil surface during sham stimulation were totally absorbed in the tube and the magnetic field induced during sham stimulation was negligible at the body surface as measured by a short dipole.[12] To blind group identity of patients the staff was divided in a treatment team and a test team. No communication about patients or study issues was allowed between teams and between patients.

Evaluations were performed at the same time of the day and began with a clinical examination of muscle tone and deep tendon reflexes followed by measurements of maximum voluntary contraction (MVC), stretch reflex, and the Hoffman reflex in random order. The individual order of biomechanical and electrophysiological tests was identical at all examinations.

*Questionnaire:* Every evening, patients self-scored the ease of daily day activities with one score only (0–10). For scoring each patient was asked to focus on the particular difficulties related to spasticity as getting out of bed, dressing and walking performance. The pre-treatment self-score value was defined to be five.

*Clinical measurements:* The same physician evaluated the spasticity bilaterally in extensor and flexor muscles at the hip, knee, and ankle joints by Ashworth score (0; no increase in tone 1; slight increase in tone giving a 'catch' 2; more marked increase in tone but limb easily flexed 3; considerable increase in tone, passive movement difficult 4; limb rigid) with a maximum score of 48 arbitrary units (AU).[10] The patellar and the Achilles tendon reflexes were evaluated according to conventional clinical grading (0; depressed or absent reflex 1; normal reflex 2; hyperreflexia 3; hyperreflexia with extended reflexogenic zone 4; hyperreflexia with extended reflexogenic zone and clonus) with a maximum score of 16 AU. The scores of muscle tone and reflex activity were combined to a single clinical score.

*Electrophysiological and biomechanical measurements:* For the electrophysiological and biomechanical measurements the subjects were seated with the foot of the most spastic extremity evaluated by the clinical measurement strapped to a pedal rotated by a motor. Angles of knee and ankle were approximately 120 degrees. For each patient the position of the chair was maintained constant during the test period. Spasticity was electrophysiologically evaluated from the stretch reflex and the maximum H-reflex ($H_{max}$) in the surface electromyogram (EMG) of the soleus muscle. The short latency stretch reflex was elicited by rotating the platform at different stretch velocities from 7.5 to 120 deg/s. Amplitudes of the reflexes were expressed as a percentage of the supramaximal direct muscle response ($M_{max}$). Stretches and releases of four degrees were delivered with a duration of 500 ms and were applied randomly with an interval of $4.0 \pm 0.2$ s. The $H_{max}$ was elicited during bipolar electrical stimulation of the posterior tibial nerve in popliteal fossa with a stimulus duration of 1.0 msec at intervals of 4.0 s. MVC of dorsi and plantar flexion at the ankle joint was measured with a strain gauge attached to the pedal as the maximal value the subject maintained for 1 s during three attempts. Bipolar EMG surface electrodes 2 cm apart were placed parallel to the tibial bone over the anterior tibial muscle and the soleus muscle just proximal to and parallel to the Achilles tendon. EMG signals were band-pass filtered (20 Hz to 2 kHz) rectified and lowpass filtered at 20 Hz and subsequently averaged over seven stretches with the position of the platform, the EMG signals, and the platform torque. All signals were displayed and stored for later analysis (signals were A/D converted at 2 kHz). For each test the threshold of the short latency reflex was defined as the minimal velocity at which a visual peak appeared in the soleus EMG. The stretch reflex amplitude was measured at a fixed stretch velocity of 88 deg/s. The stretch velocity was defined within the time interval between 10% to 90% of the 4 degrees of rotation. In the few cases where co-contraction was present the reflex measurement was repeated.

*Statistics and calculations:* Primary effect parameters were defined in a pilot study and registered the day after end of treatment (Test II).[8] The parameters were the changes (delta values) in the (1) threshold of the soleus stretch reflex; (2) in the combined clinical score of reflex activity and muscle tone, and (3) in the patients' self-score using a Bonferroni correction with a 2% limit of significance for statistical analysis. For all other differences between the treatment group and placebo group a 5% limit of significance was applied. Self-score, clinical score and difference values between the pre- and posttreatment groups were normally distributed and values (means$\pm$1SD's) were compared with paired and unpaired *t*-tests. Non-parametric statistics (Wilcoxon signed rank test, Mann-Whitney test, Spearman rank correlation coefficients) were applied for all other comparison. The protocol was approved by the local ethical committee.

## Results

Three patients from the treatment group dropped out of the study between day one and day three. One patient got a respiratory infection, the other complained of irregular heart beats 2 h after stimulation (ECG showed sinus rhythm) and the third patient had the longest transportation time and was disappointed with the treatment cost benefit relation. In all patients in the treatment group a short-lasting tight feeling like wearing a narrow ring around the mid-thoracic level was induced during stimulation. Except two episodes of brief dizziness no other side-effects were reported immediately after repetitive magnetic stimulation.

The median duration of MS from the first symtom was 12 years (range: 2–34) in the treatment group and 13 years (range: 2–30) in the placebo group. Baseline values of the clinical score of spasticity were significantly different ($P$=0.007) between the two groups (Table 2). There were no differences ($P$=0.095) at the baseline in the threshold of the stretch reflex between the two groups (Table 2).

Self-score of ease of daily day activities on the day after end of treatment (Test II) improved by 22% ($P$=0.007) in the treatment group and by 29% ($P$=0.004) in the sham stimulation (Table 2). There were no differences between the two groups, the improvement being 1.1$\pm$1.6 AU in the treatment group and 1.5$\pm$1.8 AU in the placebo group.

The clinical score (Test II) improved by 18% ($P$=0.005) after treatment and was unchanged in sham stimulation. The improvement in the treatment group as compared to control was statistically significant ($P$=0.003) the change being $-3.3\pm4.7$ AU *vs* $0.7\pm2.5$ AU, respectively (Figure 1).

The threshold of the stretch reflex (Test II) increased by 27% after treatment ($P$=0.016) and remained unchanged in sham stimulation (Table 2). The improvement of the stretch reflex threshold in treated patients as compared to sham stimulation was statistically significant ($P$=0.001) being $4.3\pm7.5$ deg/s and $-3.8\pm9.7$ deg/s, respectively (Figure 1). In the treatment group 50% (9/18) of the patients improved their self-score, 78% (14/18) their clinical score, and 50% (9/18) their stretch reflex threshold. In the placebo group 59% (10/17) of the patients improved their self-score, 59% (10/17) had an improved clinical score, and 29% (5/17) improved their threshold of the soleus stretch reflex.

Eight days after end of treatment (Test III) the threshold of the stretch reflex remained improved by 27% in the treatment group as compared to baseline ($P$=0.011). The improvement of the stretch reflex threshold after treatment was $4.4\pm7.5$ deg/s as compared to $-1.8\pm8.5$ deg/s in sham stimulation ($P<0.028$). After 16 days (Test IV) no statistically significant effect of treatment could be detected.

No differences in the amplitude of stretch reflex, the MVC of dorsi and plantar flexion at the ankle joint, and the $H_{max}/M_{max}$ ratio between the two groups were found. However, in the treatment group the $H_{max}/M_{max}$ ratio showed a tendency of decrease being 77.1 (100.0–49.4) at Test I, 70.2 (84.4–34.9) at Test II, 67.8 (89.7–41.4) at Test III ($P$=0.010), and 61.6 (100.0–35.3) at Test IV ($P$=0.025). No significant correlations were found in the treatment group (Test II) between the duration of MS and the improvement of self-score ($r$=–0.104), clinical score ($r$=–0.449), and threshold of the stretch reflex ($r$=0.024). The improvement in clinical score in the treatment group at Test II showed a tendency to an inverse relationship ($r$=–0.436, $0.05<P<0.1$) with the baseline value of the clinical score. No correlation was found

**Table 2** Primary effect parameters

| | | | *After treatment* | | |
|---|---|---|---|---|---|
| | | *Before treatment* | *1 day* | *8 days* | *16 days* |
| Self-score (arbitrary units) | treatment | 5.0$\pm$0 | 6.1$\pm$1.6[a] | 4.8$\pm$1.0 | 4.6$\pm$0.8 |
| | control | 5.0$\pm$0 | 6.5$\pm$1.8[b] | 5.8$\pm$1.6 | 5.2$\pm$1.9 |
| Clinical score (arbitrary units) | treatment | 19.8$\pm$6.1 | 16.3$\pm$6.2 [b] | 18.3$\pm$7.4 | 19.0$\pm$9.4 |
| | control | 14.4$\pm$6.8 | 13.2$\pm$7.8 | 13.5$\pm$7.3 | 13.2$\pm$9.0 |
| Stretch reflex threshold (deg/sec) | treatment | 12.6 (4.7–33.0) | 16.0 (3.1–54.7)[c] | 16.0 (3.1–54.7)[c] | 18.1 (6.2–39.6) |
| | control | 20.1 (8.2–74.1) | 16.0 (8.2–62.8) | 20.1 (8.2–54.7) | 25.1 (8.2–54.7) |

[a] $P<0.02$, [b] $P<0.01$ (paired *t*-test), [c] $P<0.02$ (Wilcoxon signed rank test)

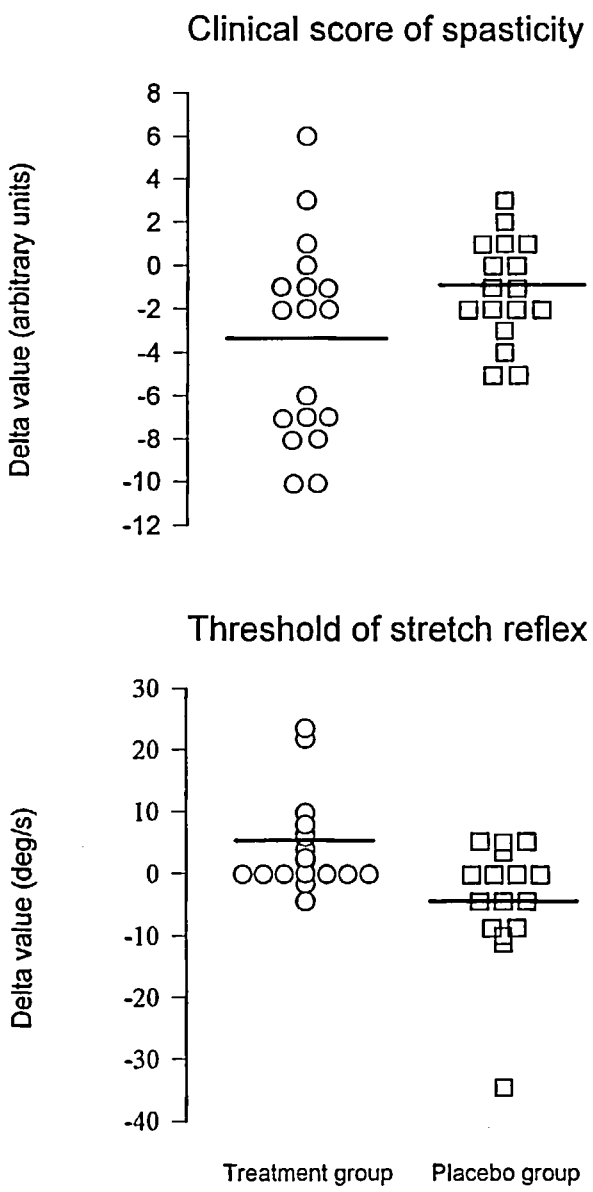


*Figure 1 Difference values of pre- and posttreatment measurements of the clinical score and of the stretch reflex threshold in magnetic stimulated (○) and sham stimulated (□) patients. The lines indicate mean values. Group differences are significant at the 0.01 level*

between improvement in stretch reflex threshold (Test II) and the baseline value of stretch reflex threshold ($r$=0.120).

## Discussion

The significant improvement in clinical score of spasticity and in stretch reflex threshold after stimulation as compared to sham stimulation shows that repetitive magnetic stimulation has beneficial effect against spasticity in patients with multiple sclerosis. The treatment regimen was repetitive magnetic stimulation for 25 min twice a day for 7 days. The effect lasted for 24 h. In addition, an antispastic effect on the stretch reflex threshold was detected 8 days after the last stimulation was given.

To use magnetic stimulation in treatment of spasticity is a new approach. Consequently, the regimen was designed to answer the question whether intensive and repetitive stimulation has any antispastic effect. The present treatment regimen can be applied in clinical neurology, but it is likely that the cost-benefit relationship is not acceptable to many patients. To reduce time expenditure and costs future studies should clarify the most optimal site of stimulation and the most efficient treatment regimen.

The significant increase of 29% in self-score in the placebo group shows that the attempt to blind the treatment to the patients was successful. In the treatment group, there was an increase of 22% in self-score. This indicates that except for the placebo effect patients experienced no additional benefit from repetitive magnetic stimulation. The clinical spasticity score at study start was significantly lower in the placebo group than in the treated group. A more severe degree of spasticity evaluated clinically could induce a type 1 error because of increased daily fluctuations or because of a more pronounced placebo effect in the patients of the treatment group. However, standard deviations of the clinical score were very similar in the treatment and the placebo group (Table 2) and there even was a statistical tendency ($P<0.1$) for an inverse relationship between baseline clinical score and the improvement of the clinical score. If anything, the difference in baseline clinical score may have resulted in an underestimation of the treatment effect. The improvement of spasticity was 18% for the clinical score and 27% for the stretch reflex threshold. 78% (14/18) of the treated patients improved clinically and 50% (9/18) improved their stretch reflex threshold. One patient in each group used drop foot stimulator. Both patients had a response close to the mean values of their groups. An analysis of the distribution of spasticity of the lower limbs in the same group of patients as used in this study has shown predominant distal spasticity.[13] It is therefore possible that the treatment effect obtained in the present study improves the walking performance by increasing the velocity of rotation at the ankle joint under the load of the body without activating the soleus stretch reflex.

Pharmacotherapy has a similar clinical success rate as repetitive magnetic stimulation. Sachais *et al* reported in a controlled multicenter trial in patients with MS a reduction in clinical muscle tone score by 15% at a daily dosage of 70–80 mg baclofen.[14] From and Heltberg in a double blind trial observed a reduction in Ashworth score by 28% and 29% after 4 weeks of treatment with baclofen (30–120 mg/daily) and diazepam (10–40 mg/daily), respectively.[15] In a double-blind crossover study Feldman *et al* found a reduction in resistance to passive movement in 65% of MS patients after 4 weeks of treatment at a daily dosage of 80 mg baclofen.[16] Many MS patients with light to moderate spasticity can not tolerate or refuse pharmacological treatment because of side-effects including drowsiness, dizziness, nausea, and muscle weakness. It is our experience that this new treatment

technique is well-tolerated by the patients and have no serious side-effects according to the patients. To offer this form of treatment it should be safe. In our preliminary study there was one episode of brief dizziness but no long term side-effects have been reported.[8] In the present study two episodes of brief dizziness were reported immediately after treatment sessions and one episode of irregular heart beats 2 h after a treatment session might indicate a systemic haemodynamic effect. However, the two episodes of dizziness were probably of ortostatic origin and the feeling of irregular heart beats could not be confirmed by electrocardiography. In a safety study four of the active treated patients were monitored with ECG, pulse, and blood pressure measurements during 25 min of repetitive magnetic stimulation as described in the protocol and no changes were observed. Although cardiac involvement was not observed we recommend a more caudal placement of the magnetic coil in future studies.

Although the mechanisms behind the effect of repetitive magnetic stimulation are obscure, various proposals can be suggested. The increase of the stretch reflex threshold obtained following magnetic stimulation at the thoracic level might result from decreased depolarisation of the soleus motoneurons due to suprasegmental influence. Descending volley of impulses due to an afferent musculocutaneous inflow during magnetic stimulation could produce the effect. In fact, a massive musculocutaneous inflow during stimulation is present. Magnetic stimulation evokes contraction of mid-thoracic paravertebral muscles and of intercostal muscles resulting in a tightening feeling around the chest. It is unknown whether magnetic stimulation excites muscle tissue directly or by primary nerve stimulation. Other methods to external modulation of the nervous system is described. Studies by MF Levin and co-workers had demonstrated that TENS decreases spasticity and improves motor control in spastic patients.[5,17] Since the gate control theory suggested that activity in large mechanoreceptive fibers will presynaptically inhibit the activity of thin nociceptive afferents, the optimal parameters for TENS have been low intensity (to primarily excite large diameter fibers with low resistance to current flow) and high frequency (>40 Hz). This type of nerve stimulation differs from the magnetic stimulation by the fact that the nerve stimulation evokes no motor response but a tingling sensation localized to the site of stimulation. In addition to TENS, high frequency electrical stimulation of the spinal cord by epidural implanted electrodes at thoracic level has been used in treatment of spasticity. Several hypotheses have been put forward to explain the neurological improvements seen during epidural spinal cord stimulation. Read *et al* found it possible to record direct muscle responses in the rectus abdominis and the thigh muscles during high frequency epidural stimulation (7–120 Hz) although the epidural electrodes were placed above the segmental origin of the thigh muscles involved.[18] They concluded that both a direct excitation of the anterior horn neurons and a stimulation of the descending pathways occurred. It was suggested that the descending inhibitory pathways might be stimulated and in consequence depression of local reflexes from voluntary muscles and bladder was seen and hence explains the improvements. There is some experimental evidence for this hypothesis. Foreman *et al* showed short term effects (150 ms) of dorsal column stimulation in inhibition of high-threshold spinothalamic tract neurons at lower segmental levels in monkeys.[19] Siegfried *et al* observed in unanaesthetized decerebrate cats that dorsal column stimulation with 50 Hz for 1–30 s at thoracic level caused up to 10 min lasting reduction of monosynaptic reflexes, a decrease in firing frequency of motoneurons, and an increased repetitive discharge of Renshaw cells at lumbar level.[20] A different hypothesis can be constructed on the basis of a study performed by Iggo *et al*.[21] They found a class of neurons in paralysed cats and monkeys responsive to cutaneous mechanoreceptors and nociceptive afferent input. Noxiously-induced persistent discharge of the neurons could be inhibited by electrical stimuli delivered to the peripheral nerve or by electrical stimulation of the skin. This effect could be mimicked by electrical stimulation of the dorsal columns where stimulus frequencies between 10 and 50 Hz were sufficient to cause almost complete suppression of the neurons. A well recognized clinical phenomenon is the relationship between a full bladder and increased lower limb spasticity. Spasticity is reduced after changing the afferent input by emptying the bladder. This clinical observation has been confirmed electrophysiologically.[22] In summary, changes in the afferent input can reduce spasticity. Mechanisms as described above could be involved in the short-lasting antispastic effect found in the present study.

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