Effects of intermittent theta burst stimulation on spasticity after spinal cord injury

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Abstract

Purpose: Spasticity is a common disorder in patients with spinal cord injury (SCI). The aim of this study was to investigate whether intermittent theta burst stimulation (iTBS), a safe, non-invasive and well-tolerated protocol of excitatory repetitive transcranial magnetic stimulation (rTMS), is effective in modulating spasticity in SCI patients.

Methods: In this randomized, double-blind, crossover, sham-controlled study, ten subjects with incomplete cervical or thoracic SCI received 10 days of daily sessions of real or sham iTBS. The H/M amplitude ratio of the Soleus H reflex, the amplitude of the motor evoked potentials (MEPs) at rest and during background contraction, as well as Modified Ashworth Scale (MAS) and the Spinal Cord Injury Assessment Tool for Spasticity (SCAT) were compared before and after the stimulation protocols.

Results: Patients receiving real iTBS showed significant increased resting and active MEPs amplitude and a significant reduction of the H/M amplitude ratio. In these patients also the MAS and SCAT scores were significantly reduced after treatment. These changes persisted up to 1 week after the end of the iTBS treatment, and were not observed under the sham-TBS condition.

Conclusion: These findings suggest that iTBS may be a promising therapeutic tool for the spasticity in SCI patients.

Keywords: Intermittent theta burst stimulation, spinal cord injury, spasticity, motor evoked potential, H/M amplitude ratio, Modified Ashworth Scale, Spinal Cord Injury Assessment Tool for Spasticity

1. Introduction

Techniques able to drive brain plasticity, such as the repetitive transcranial magnetic stimulation (rTMS), may be of great interest in rehabilitation of spasticity.

It has been shown that high-frequency (HF) rTMS induced significant reduction in the spasticity in the lower extremities in incomplete SCI (Kumru et al., 2010; Nardone et al., 2014). In the first study 20 Hz rTMS was applied on the vertex for 5 days (Kumru et al., 2010). The patients reported after the last rTMS session and during 1 week of follow-up significant improvement in spasticity, which was assesses by Modified Ashworth Scale (MAS), Visual Analogue Scale for Spasticity, Modified Penn Spasm Frequency Scale, and Spinal Cord Injury Spasticity Evaluation Tool. Notably, this study failed to find changes in the examined measures of corticospinal and segmental
excitability (H/M amplitude ratio, T reflex, and withdrawal reflex). In a more recent study of the same research group, motor scores in lower extremities improved significantly in the group who received real rTMS, while MAS did not change significantly after 4 weeks of real rTMS (Kumru et al., 2016).

In the present study, our aim was to assess whether a different rTMS protocol may have significant clinical beneficial effects in the treatment of lower limb spasticity in SCI patients.

Theta burst stimulation (TBS) is a rTMS stimulation protocol that may have several advantages in these patients because it employs low intensities, and was found to have a robust and long-lasting effect both in normal subjects (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) and in stroke patients (Di Lazzaro et al., 2006; Talelli et al., 2007). Different patterns of delivery of TBS (continuous versus intermittent) produce opposite effects on synaptic efficiency of the stimulated motor cortex (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Cooke & Bliss, 2006). The paradigm named intermittent TBS (iTBS) produces a consistent long-term potentiation (LTP)-like effect, causing a prolonged increase of motor cortex excitability (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). This protocol produced a pronounced enhancement of corticospinal output in a chronic stroke patient in whom it was recorded directly the descending activity evoked by motor cortex stimulation (Di Lazzaro et al., 2006).

If corticospinal excitability can be enhanced by these procedures then there are important implications for the development of therapeutical strategies based on TMS techniques in patients with spinal cord disorders. Therefore, we tested in the study the effect of iTBS on spasticity in SCI patients.

2. Materials and methods

2.1. Patients

Ten subjects (mean age 42.8 years, range 24–65 years, seven males and three females, nine right-handed) with chronic incomplete cervical or thoracic SCI, classified as grades C or D according to the American Spinal Cord Injury Association Impairment Scale (Marino et al., 2002) were enrolled in the study.

Inclusion criteria were: a) spasticity affecting lower limbs with a Modified Ashworth Scale (MAS) (Bohannon & Smith, 1987) >4.5; b) ability to give informed consent and comprehend instructions. Exclusion criteria were: a) contraindications to TMS such as metal head implants, or lack of tolerance to TMS; b) concomitant neurological conditions, including any history of epilepsy and polyneuropathies; c) joint-related limitation of passive range of movement; advanced liver, kidney, cardiac or pulmonary disease; d) history of significant alcohol or drug abuse.

Clinical and demographic features of the patients are shown in Table 1.

All the eligible patients were taking antispastic medication (Baclofen 15–50 mg/die) and all received physical therapy, which were not modified during the study and 2 months before and after the stimulation. The patients did not receive any other neurological medication before and during the course of the intervention. The study was performed according to the declaration of Helsinki and approved by the Ethics Committee. Patients gave their written informed consent before participation and all personal data were maintained confidential.

<table>
<thead>
<tr>
<th>Patients</th>
<th>A(y)</th>
<th>G</th>
<th>Aetiology</th>
<th>Time since SCI (y)</th>
<th>Level/ASIA</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>M</td>
<td>Disc prolaps</td>
<td>17</td>
<td>C6/D</td>
<td>BAC 15 mg/d</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>F</td>
<td>Fracture</td>
<td>4</td>
<td>C6/C</td>
<td>BAC 50 mg/d</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>M</td>
<td>Fracture</td>
<td>6</td>
<td>C5/D</td>
<td>BAC 45 mg/d</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>M</td>
<td>Fracture</td>
<td>4</td>
<td>C7/D</td>
<td>BAC 10 mg/d</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>M</td>
<td>Fracture</td>
<td>8</td>
<td>T4/D</td>
<td>BAC 15 mg/d</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>F</td>
<td>Fracture</td>
<td>3</td>
<td>T8/C</td>
<td>BAC 30 mg/d</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>M</td>
<td>Fracture</td>
<td>13</td>
<td>T4/C</td>
<td>BAC 15 mg/d</td>
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<tr>
<td>8</td>
<td>32</td>
<td>M</td>
<td>Fracture</td>
<td>6</td>
<td>C6/C</td>
<td>BAC 25 mg/d</td>
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<tr>
<td>9</td>
<td>46</td>
<td>M</td>
<td>Fracture</td>
<td>8</td>
<td>T6/D</td>
<td>BAC 15 mg/d</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
<td>F</td>
<td>Fracture</td>
<td>14</td>
<td>C7/D</td>
<td>BAC 5 mg/d</td>
</tr>
</tbody>
</table>

Legend: A = age; G = gender; y = years; SCI = spinal cord injury; ASIA = American Spinal Cord Injury Association Impairment Scale; BAC = Baclofen.
2.2. Experimental procedures

Motor-evoked potentials (MEPs), the soleus motor action potentials (M-wave) and H reflex were recorded by silver–silver chloride (Ag–AgCl) surface cup electrodes. The active electrode was placed over the Soleus muscle belly, the reference electrode was placed 5 cm distal. Tests were carried out with the patient lying in the prone position and the feet suspended over a pillow with the knees flexed at about 45° and the ankles at about 90°. M-wave and H reflex were evoked by electrical stimulation of the tibial nerve through a bipolar electrode placed in the popliteal fossa (squared pulse, 1 ms duration, Digitimer electrical stimulator). The H-reflex responses were measured as the peak-to-peak amplitude of the non-rectified H-reflex. Hmax was selected by increasing stimulus intensity until maximum amplitude H responses were obtained. Ten H responses were recorded at this stimulus intensity and the one of greatest amplitude was chosen as Hmax. Responses were amplified through a Digitimer D360 amplifier (Digitimer, Welwyn Garden City, Herfordshire, UK), band pass filtered between 2 Hz and 10 kHz, sampled at a rate of 5 kHz and recorded on a PC with Signal 3 software (Cambridge Electronic Devices, Cambridge, UK).

MEPs were evoked using a Magstim Rapid 2 magnetic stimulator (Magstim Company, Whitland, Wales, UK) connected with a figure-of-eight coil with external loop diameter of 70 mm. The position of the coil was adjusted to find the optimal scalp site to evoke motor responses in the contralateral Soleus muscle (‘motor hot spot’) at the beginning of each experimental session and marked over the patients scalp with a dermographic pencil. The ‘hot spot’ for the contralateral Soleus muscle referred to the mid-saggital line of the scalp. If no MEP was detectable even from the contralateral leg the coil was held tangentially to the scalp with its centre placed 1 cm ahead and 1 cm lateral from CZ (10–20 EEG system). In these cases, stimulation intensity was set to 50% of the maximum stimulator output (MSO).

For the sham stimulation, iTBS was delivered (15% of MSO) with the coil held close over the motor area determined as for real stimulation but tilted approximately to 90° so that no current was induced in the brain (Wassermann & Lisanby, 2001). Patients were initially randomized to undergo either real iTBS (5 patients) or sham iTBS (5 patients). The 5 patients who underwent sham iTBS first were subsequently crossed over to undergo real iTBS, following a ≥ 2 months washout period. Patients and investigators (except the rTMS operator) were blinded to the form of stimulation.

All the patients were stimulated once a day for five consecutive days for 2 weeks. The treating physician, who was aware of group allocation because he had to set up the stimulation protocol, was instructed not to talk to both the patients and the assessing physicians about the stimulation procedure.

For the clinical evaluation of spasticity, we used MAS and SCAT (Benz, Hornby, Bode, Scheidt, & Schmit, 2005). For each patient, the MAS was scored in three joints of the studied limb with a six-point (0, 1, 1+, 2, 3, 4) scale: ankle (flexion-extension and pronation-supination of the foot), knee (flexion-extension of the leg), hip (abduction-adduction of the limb). The study was limited to the leg contralateral to the dominant hemisphere.

Mean peak-to-peak MEP amplitude (20 trials) were measured during rest (rMEP) bilaterally and with background muscle contraction of about 15 of the maximum (aMEP). MAS, SCAT, Hmax/Mmax amplitude ratio, resting and active MEP amplitudes were evaluated by two neurologists who were unaware of group allocation, on the first day of treatment, before (T0) and immediately after (T1) the first session of iTBS, immediately after the last stimulation session (T2), one (T3) and four (T4) weeks later.
2.3. Statistical analysis

For statistical analysis we used the software R (R Core Team (2015)). Tests were conducted using the package nparLD (Noguchi, Gel, Brunner, & Konietzke, 2012). For the creation of figures we used the package ggplot2 (Wickham, 2009).

We set alpha to be 0.05. For each of the five outcome variables MAS, SCAT, H/M amplitude ratio, resting MEP and active MEP we first performed an ANOVA-type test for a time effect and a treatment \times time interaction effect at alpha/10 respectively. If the interaction effect was significant we conducted a test for this variable for each of the two treatment conditions individually at alpha/20 respectively. This strategy controls the probability of a type 1 error. If the interaction effect was significant for a variable, we do not report the overall time effect in the results since the individual tests for each group provide more information.

As a measure of effect we used the relative treatment effect (RTE) provided by nparLD. The RTE can be interpreted in the following way:

For comparisons between two groups, A and B, the RTE for A describes the probability that a randomly drawn subject from group A scores higher on the outcome variable than a randomly drawn subject from group B plus half the probability that a randomly drawn subject from group A scores the exact same score on the outcome variable as a randomly drawn subject from group B. The RTE thus lies between 0 and 1, with 0.5 meaning no effect and 0 and 1 meaning complete separation of the two groups. For comparisons with more than two groups the RTE for a group is the probability that a random subject drawn from this group scores higher than a random subject drawn from the entire sample plus half the probability that a random subject drawn from this group scores exactly the same on the outcome variable than a subject randomly drawn from the entire sample. In this case the RTE lies between 1/(2N) and 1- 1/(2N), where N is the number of groups.

3. Results

None of the subjects reported any adverse side effects.

For MAS there was a significant treatment \times time interaction effect (F(1.6, \infty) = 27.97; p < 0.001; RTEs: active:T0 = 0.58, active:T1 = 0.50, active:T2 = 0.17, active:T3 = 0.25, active:T4 = 0.56, sham:T0 = 0.60, sham:T1 = 0.59, sham:T2 = 0.58, sham:T3 = 0.58, sham:T4 = 0.59). There was a significant time effect in the active group (F(1.6, \infty) = 49.76; p < 0.001; RTEs: T0 = 0.67, T1 = 0.59, T2 = 0.24, T3 = 0.35, T4 = 0.65) indicating a decrease in MAS followed by a return to baseline. There was no significant time effect in the sham group (F(1.8, \infty) = 0.84; p = 1; RTEs: T0 = 0.51, T1 = 0.50, T2 = 0.49, T3 = 0.50, T4 = 0.50) (Fig. 1).

For SCAT there was a significant treatment \times time interaction effect (F(2, \infty) = 35.50; p < 0.001; RTEs: active:T0 = 0.57, active:T1 = 0.52, active:T2 = 0.23, active:T3 = 0.27, active:T4 = 0.53, sham:T0 0 0.59, sham:T1 = 0.59, sham:T2 = 0.56, sham:T3 = 0.56, sham:T4 = 0.58). There was a significant time effect in the active group (F(2.5, \infty) = 69.33; p < 0.001; RTEs: T0 = 0.65, T1 = 0.60, T2 = 0.29, T3 = 0.35, T4 = 0.61) indicating a decrease in SCAT followed by a return to baseline. There was no significant time effect for the sham condition (F(1.5, \infty) = 1.8; p = 1; T0 = 0.51, T1 = 0.51, T2 = 0.49, T3 = 0.49, T4 = 0.50) (Fig. 2).

For the $H_{\max}/M_{\max}$ amplitude ratio there was a significant treatment \times time interaction effect (F(1.6, \infty) = 46.64; p < 0.001; RTEs: active:T0 = 0.70, active:T1 = 0.59, active:T2 = 0.08, active:T3 = 0.18,
Fig. 2. Box plots illustrating median Spinal Cord Injury Assessment Tool for Spasticity (SCAT) score at the 5 time points after real and sham iTBS. The SCAT was significantly decreased at T2 and T3.

active:T4 = 0.61, sham:T0 = 0.58, sham:T1 = 0.58, sham:T2 = 0.55, sham:T3 = 0.56, sham:T4 = 0.57. There was a significant time effect for the active condition (F(1,8,∞) = 73.53; p < 0.001; RTEs: T0 = 0.74, T1 = 0.65, T2 = 0.15, T3 = 0.29, T4 = 0.67) indicating a decrease in Hmax/Mmax amplitude ratio followed by a return to baseline. There was no significant time effect for the sham condition (F(2,1,∞) = 0.88; p = 1; RTEs: T0 = 0.51, T1 = 0.51, T2 = 0.49, T3 = 0.49, T4 = 0.50) (Fig. 3).

For resting MEP there was a significant treatment × time interaction effect (F(2,5,∞) = 19.84; p < 0.001; RTEs: active:T0 = 0.45, active:T1 = 0.67, active:T2 = 0.71, active:T3 = 0.49, active:T4 = 0.44, sham:T0 = 0.43, sham:T1 = 0.47, sham:T2 = 0.44, sham:T3 = 0.49, sham:T4 = 0.40). There was a significant time effect for the active condition (F(1,6,∞) = 34.78; p < 0.001; RTEs: T0 = 0.40, T1 = 0.61, T2 = 0.67, T3 = 0.44, T4 = 0.39) indicating an increase in resting MEP followed by a return to baseline. There was no significant time effect for the sham condition (F(2,4,∞) = 3.40; p = 0.518; RTEs: T0 = 0.48, T1 = 0.53, T2 = 0.50, T3 = 0.54, T4 = 0.45) (Fig. 4).

For active MEP there was a significant treatment × time interaction effect (F(2,4,∞) = 13.44; p < 0.001; RTEs: active:T0 = 0.46, active:T1 = 0.63, active:T2 = 0.66, active:T3 = 0.51, active:T4 = 0.47, sham:T = 0.46, sham:T1 = 0.48, sham:T2 = 0.46, sham:T3 = 0.44, sham:T4 = 0.44). There was a significant time effect for the active condition (F(1,5,∞) = 28.34; p < 0.001; RTEs: T0 = 0.42, T1 = 0.58, T2 = 0.61, T3 = 0.46, T4 = 0.43) indicating an increase in active MEP followed by a return to baseline. There was no significant time effect for the sham condition (F(1,8,∞) = 1.97; p = 1; RTEs: T0 = 0.52, T1 = 0.53, T2 = 0.51, T3 = 0.47, T4 = 0.48) (Fig. 5).

In summary, the most salient findings were: 1) a significant decrease of the MAS and SCAT scores at T2 and T3; 2) a significant decrease of the Hmax/Mmax amplitude ratio at T2 and T3; 3) a significant increase of the resting and active MEP amplitudes at T1 and T2.

4. Discussion

RTMS techniques, possibly in combination with rehabilitation therapies, hold promise for facilitating
neuromodulation in subjects with corticospinal tract lesions. This study first showed that multiple sessions of iTBS over the M1 caused a reduction of spasticity in subjects with SCI lasting at least 1 week after the treatment.

Our findings are consistent with those of other recent TMS studies. In fact, iTBS applied to the M1 was found to improve lower limbs spasticity in patients with multiple sclerosis. Resting-state functional magnetic resonance imaging (fMRI) showed that functional reorganization of M1 in both hemispheres may underlie the effect of iTBS (Boutiere et al., 2016). In another study, iTBS on the affected hemisphere reduced transiently post-stroke upper-limb spasticity (Kim, Shin, Jung, Jung, & Kim, 2015).

ITBS is a non-invasive and painless procedure able to modulate cortical excitability of motor areas and induce changes on the descending corticospinal tract.

Furthermore, we have demonstrated in this study that, also in SCI subjects, iTBS results in an increase in motor cortex excitability, which may facilitate activity in descending pathways.

The increase in cortical excitability induced by iTBS confirms that this stimulation protocol may induce LTP-like changes at synaptic connections in the motor cortex (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Di Lazzaro et al., 2008). iTBS may thus modulate transmission in specific spinal circuitries through changes in corticospinal drive. The enhancement of motor cortex excitability by iTBS results in a significant modulation of spinal cord excitability (Siebner & Rothwell, 2003; Hiscock, Miller, Rothwell, & Tallis, 2008).

Table 2: Clinical and electrophysiological findings at the 5 time points in the after active and sham intermittent theta burst stimulation (iTBS) (mean ± standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>Active iTBS</th>
<th>Sham iTBS</th>
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<tbody>
<tr>
<td>T0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAS</td>
<td>6.4 ± 2.46</td>
<td>6.4 ± 2.27</td>
</tr>
<tr>
<td>SCAT</td>
<td>5.7 ± 1.55</td>
<td>5.5 ± 2.44</td>
</tr>
<tr>
<td>Hmax</td>
<td>0.66 ± 0.056</td>
<td>0.63 ± 0.050</td>
</tr>
<tr>
<td>Mmax</td>
<td>1.36 ± 1.43</td>
<td>1.33 ± 1.24</td>
</tr>
<tr>
<td>Hmax/Mmax</td>
<td>0.50 ± 0.012</td>
<td>0.49 ± 0.011</td>
</tr>
<tr>
<td>rMEP</td>
<td>0.32 ± 0.02</td>
<td>0.26 ± 0.02</td>
</tr>
<tr>
<td>aMEP</td>
<td>1.41 ± 0.05</td>
<td>1.39 ± 0.05</td>
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</tbody>
</table>

Legend: MAS = Modified Ashworth Scale; SCAT = Spinal Cord Injury Assessment Tool for Spasticity; Hmax = maximal H-reflex; Mmax = maximal M wave amplitude; rMEP = resting motor evoked potentials; aMEP = active motor evoked potentials.
The decrease in spasticity induced by iTBS may be due to a strengthening of the descending projections with segmental effect of spinal interneurons (Valero-Cabre, Oliveri, Gangitano, & Pascual-Leone, 2001). Increasing the excitability of the M1 would modify descending corticospinal influences and increase inhibitory input, which would then reduce segmental spinal excitability and thus reduce limb spasticity in patients with incomplete SCI. rTMS might strengthen descending projections between the motor cortex and inhibitory spinal interneuronal circuits, thus reducing leg spasticity (Nardone et al., 2014).

The results of this study suggest that the behavioural beneficial effects of iTBS may outlast the initial increase in corticospinal excitability; iTBS may facilitate strengthening of relevant synapses if they are repeatedly used during subsequent testing.

A novel finding of this study was that we first found in subjects with SCI, even if only after multiple sessions, a significant effect of brain stimulation on the H/M amplitude ratio, which is a reliable neurophysiological index of spinal excitability.

Single sessions of 5 Hz rTMS were found to be able to reduce H/M Soleus H-reflex amplitude ratio in healthy subjects (Perez, Lungholt, & Nielsen, 2005) and patients with multiple sclerosis (Centonze et al., 2007), while after a single session of iTBS also previous studies failed to show any modification (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Mori et al., 2010). The different stimulation intensities used in these two TMS protocols might explain this finding. The higher intensity used for 5 Hz stimulation (90% of the RMT vs. 80% of AMT) is probably able to recruit a higher number of motor neurons of the corticospinal tract and, therefore, exert a stronger effect on spinal circuits. It has been therefore hypothesized that iTBS may induce long-lasting modifications of spinal circuits only when applied during several days, due to changes in the excitability of the cortical and spinal networks involved (Mori et al., 2010).

Anyway, iTBS may lead to lasting changes by varying the connectivity between motor cortex and spinal cord circuits (Di Lazzaro et al., 2005). Interestingly, iTBS over the M1 produces a pronounced increase in the excitability of cortical circuits generating the later I-waves (Di Lazzaro et al., 2004, 2005, 2008), which represent synchronous activity of corticospinal axons originating from trans-synaptic activation of corticospinal cells. In fact, late I-waves can have a crucial role in determining the response to TMS. The contribution of the late I-waves to the firing of the α-motoneuronal pool that is disproportional to its contribution to the descending volley. Although late I-waves might make a relatively small contribution to the descending volley, they can have a substantial effect on recruitment at the α-motoneuron pool. In fact, late I-waves increase the descending volley by 23.5% but increased the proportion of motoneurons that fired by 567% (Tickbroom, 2011).

The present pilot study has several limitations. The sample size was relatively small and further studies in a large cohort of patients are needed to confirm these preliminary results. Moreover, even if only patients who are taking baclofen were enrolled, the stimulation/evaluation sessions were not scheduled in relationship to the Baclofen intake.

Nevertheless, our findings clearly suggest that iTBS can be considered as promising tool for the treatment of spasticity also in patients with traumatic SCI patients and perhaps other pathological conditions. In comparison with standard rTMS protocols, iTBS represents a more feasible approach because of lower stimulation intensity and shorter duration of application in each single session.

Acknowledgments

None.

References


