CASE REPORT

Therapeutic Application of Transcranial Magnetic Stimulation Combined with Rehabilitative Training for Incomplete Spinal Cord Injury: A Case Report

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Background: Only a few researchers have therapeutically applied transcranial magnetic stimulation (TMS) for patients with spinal cord injury. The purpose of this case study was to evaluate the safety, feasibility, and efficacy of therapeutic TMS combined with rehabilitative training for a patient with tetraparesis resulting from incomplete spinal cord injury. Case: An 82-year-old male patient with incomplete spinal cord injury was admitted to our department for long-term rehabilitation. Eighteen days prior to admission, the patient sustained the injury in a fall. At admission to our department, the patient was diagnosed as having injury of the spinal cord at the C6 level. From the 76th day after admission, when the patient was considered to have attained a plateau state of recovery, application of therapeutic TMS was initiated using a double-cone coil. Two 15-min sessions of 10-Hz TMS were scheduled for daily application. Simultaneously, rehabilitative training was continuously provided. This patient received a total of 30 sessions of TMS over 19 days. Neither adverse effects nor deterioration of neurological symptoms was recognized during the intervention period. With this application of TMS, some improvements were evident in the American Spinal Injury Association motor score, the knee muscle strength, and the calf circumference. Discussion: This case study demonstrated the safety and feasibility of TMS combined with rehabilitative training in a patient with incomplete spinal cord injury. Our protocol featuring TMS might constitute a novel neurorehabilitation intervention for such patients; however, the efficacy of the protocol should be confirmed in a large number of patients.

Key words: rehabilitative training; spinal cord injury; tetraparesis; transcranial magnetic stimulation; upper motor neurons

INTRODUCTION

Spinal cord injury (SCI) is a highly debilitating neurological condition that can be caused either by trauma or by a disease such as a tumor.1,2) In Japan, there are reportedly 5000 new cases each year. SCI results in the disruption of neuronal circuitry leading to the partial or complete loss of motor control, sensory input, and autonomic function. Tetraparesis and paraparesis are major neurological symptoms frequently seen in patients with SCI. However, SCI still lacks effective therapeutic strategies. To date, no effective therapeutic intervention is available that can entirely restore neurological deficits in SCI. Therefore, SCI can be a cause of permanent disability, leading to a significant financial burden and distress to the affected families.3) Transcranial magnetic stimulation (TMS) is a painless and safe procedure involving noninvasive brain stimulation.4,5) If TMS is applied in a repetitive manner, it can modulate local cortical neural excitability. It has been reported that the effect of repetitive TMS can range from upregulation to downregulation of neural activity, depending on the frequency of the stimulation. Recently, repetitive TMS has been introduced as a therapeutic tool for some brain diseases such as depression, stroke, and Parkinson's disease, and has proved to be safe and
beneficial for such patients.\(^6,7\) In addition to its neuromodulation effect targeting cerebral cortex, application of TMS is expected to stimulate upper motor neurons, including the spinal cord, and accelerate neural function of longitudinal neurons. However, only a few researchers have therapeutically applied TMS for patients with SCI.\(^8\)–\(^12\) Combined application of TMS and rehabilitative training might facilitate and accelerate motor functional recovery in patients with SCI by neural facilitation of affected upper motor neurons. Therefore, the purpose of this case study was to provide an initial evaluation of the safety, feasibility, and efficacy of therapeutic TMS combined with rehabilitative training for a patient with tetraparesis resulting from incomplete SCI.

**CASE REPORT**

An 82-year-old right-handed male patient with incomplete SCI was admitted to our department to undergo long-term rehabilitation. Eighteen days prior to admission to our department, the patient sustained a SCI in a fall. On the day of the injury, he was emergently admitted to an acute general hospital and was managed conservatively without any surgical intervention. On admission to the acute hospital, neither paralysis of the respiratory muscles nor autonomic hyperreflexia was noted. On neurological examination at admission to our department, the patient’s voluntary movement was disturbed in all four limbs to some extent, indicating the presence of tetraparesis. In particular, extension of the elbow joint, extension of the wrist joint, and plantar and dorsiflexion of the ankle joint were markedly impaired. Muscle tonus of the bilateral lower limbs was generally increased, and the spasticity of the plantar flexor muscle was bilaterally graded as modified Ashworth scale 2. In terms of sensory deficits, slight numbness was noted in distal portions of bilateral hand fingers. The patient was not able to stand up without help and needed a wheelchair. Moreover, he needed some physical assistance to perform activities of daily living (ADL) such as transferring from bed to a wheelchair, toileting, and bathing. The mental and psychiatric status was not disturbed. Based on such neurological findings, this patient was diagnosed as having injury of the spinal cord at the C6 level, and was classified as C6A using the Zancolli classification and as D on the American Spinal Injury Association (ASIA) impairment scale. The findings on sagittal plane spinal MRI-T2 weighted images on the day of admission to the acute hospital, which showed cervical cord compression at the level of C2/3, C3/4, and C4/5, was compatible with these neurological finding (Fig. 1). As a medical comorbidity, the patient had been diagnosed with diabetes mellitus and had been treated with oral hypoglycemic agents for more than 5 years.

After admission to our department, the patient initially underwent conventional rehabilitative training consisting of daily physical and occupational therapy. With this training, the patient showed some functional recovery of motor systems (Table 1). However, no apparent functional improvement was found in the ASIA motor score during the period between the 69th day and 76th day after admission. Therefore, it is possible that the patient had mostly attained a plateau state at this point. Combined with rehabilitative training, from the 76th day after admission, TMS was therapeutically applied to this patient. Two 15-min sessions of TMS were applied daily for 19 days, except for two Saturdays and two Sundays (TMS was applied for 15 days in total).
Overall, 30 TMS sessions were applied during the period. Further medical interviews and examinations confirmed the absence of pathological conditions that could be considered a contraindication for TMS, such as intracranial implants, a cardiac pacemaker, or a recent history of seizure.\(^{13}\)

The study protocol, including TMS application, was approved by the ethics committee of our institution (International University of Health and Welfare Ichikawa Hospital). This case study was carried out in compliance with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from the patient before the application of TMS.

**Application of TMS**

Therapeutic TMS was delivered using a MagPro R30 stimulator (MagVenture Company, Farum, Denmark) equipped with a double-cone coil (Cool D-B80, each wing measuring 80 mm in diameter) with the patient in a chair (Fig. 2). In a 15-min TMS session, 10-Hz TMS was repetitively applied in 10-s trains (100 pulses per train) with 50-s intervals between trains (1500 pulses per session). During the period of TMS application, 3000 pulses of TMS were provided daily. This study defined the optimal site of stimulation on the skull as the position on the midsagittal plane where the largest motor evoked potential in the tibialis anterior (TA) muscle of the less affected (left) lower limb was elicited on surface electromyography. The center of contact between the two circles of the coils was placed vertically over the determined stimulation site on the midsagittal plane, aiming to predominantly stimulate bilateral leg motor areas. Because double-cone coils reportedly generate effective magnetic fields in deep brain regions, the TMS delivered by the coil can stimulate leg motor areas that are located deep within the intercerebral fissure.\(^{14,15}\) The resting motor threshold (MT) of the TA muscle of the less affected lower limb was defined as the minimum stimulus intensity that produced a minimal motor evoked response of the muscle at rest. According to the measured resting MT level, the intensity of the stimulation was set at 110% of the resting MT of the muscle. A rehabilitation physician clinically monitored the patient throughout the TMS sessions.

**Provision of Rehabilitative Training**

In parallel with TMS application, rehabilitative training, such as physical and occupational therapy, was continuously provided as one-to-one training by the therapists at our department. The training program combined with TMS was almost the same as that provided at our department prior to TMS application. The program of physical therapy consisted of stretching of the muscles in the lower limbs and the trunk, muscle strengthening exercise of lower limb muscles, sitting in a wheelchair, standing, and gait training wearing ankle–foot orthosis. The program of occupational therapy mainly involved stretching of the muscles in the upper limbs and the shoulder, repetitive task practice using upper limbs, and training of ADL. During the period of TMS application, a 120-min training session consisting of physical and occupational therapy was provided daily. The program was modified following motor functional improvement of the affected limbs.

**Clinical Evaluation of Neurological and Physical Functions**

For this patient, some clinical measures were applied to investigate the influence on neurological and physical functions of this combined protocol featuring TMS application. As main measures, ASIA motor and sensory scores were evaluated at several time points, such as before the first and after the last session of TMS. These ASIA scores are commonly used to describe the severity of SCI, recovery after SCI, and the response to therapeutic intervention in patients with SCI.\(^{16}\) The maximum score is 100 points for the motor score and 224 points for the sensory score. To assess muscle power and the volume of the lower limbs, knee extensor muscle strength and maximum calf circumference of bilateral lower legs were manually measured serially. The spasticity of planter flexor muscles was evaluated using the modified Ashworth scale. To evaluate physical performance comprehensively, including the level of ADL, the Short Physical Performance Battery (SPPB), the Ability for Basic Movement Scale-2 (ABMS-2) score, and the Functional Independence Measure (FIM) were estimated before and after the application of TMS.\(^{17–19}\) For these three evaluations, a higher score reflects a better function (maximum score: 12 points for SPPB, 30 points for ABMS-2 and 126 points for FIM).

**RESULTS**

The proposed 15-day protocol featuring TMS of 110% of resting MT intensity was successfully completed for this patient. Throughout the 15-day application of TMS combined with rehabilitative training, the patient reported no adverse event and showed no deterioration of neurological or physical symptoms. No significant changes in vital signs were observed throughout the intervention. During each TMS session, apparent movements with a frequency of 10 Hz were evident not only in bilateral lower limbs but also in bilateral upper limbs, including hands.
After this 15-day application of TMS, some improvements were noted in the applied neurological and physical measures. Primarily, an increase of >10% was found in the ASIA motor score bilaterally at the end of TMS application (Table 1). This increase in score reflected a motor functional improvement in the upper limbs. Moreover, increases in knee extensor muscle strength and maximum calf circumference were observed in the bilateral lower legs during the period. The rate of change of the ASIA total motor score was −0.14 points per day between the 69th and 76th day after admission and 0.44 points per day between the 69th and 76th day after admission. This difference in the rate of change of the score indicated that the period between the 76th and 94th day after admission could represent a plateau state. For this patient, TMS application did not reduce the spasticity in the bilateral legs. Even after the last session of TMS on the 94th day after admission, the ASIA motor score in the right side increased slightly, which reflected the motor functional improvement in the right upper limb. Furthermore, the knee extensor muscle strength in the left lower limb increased after the last session of TMS, although the increase in the muscle strength was not reflected in ASIA motor score. With regard to ADL, the patient became able to transfer from a bed to a wheelchair and to urinate in the rest room with less assistance at discharge from the hospital.

### DISCUSSION

Our proposed protocol featuring 10-Hz TMS and rehabilitative training was safely completed and produced some motor functional recovery in a SCI patient with tetraparesis. So far, to the best of our knowledge, only a few researchers have applied TMS for SCI patients.8–12 Among them, two studies examined the effects of TMS on lower limb motor functions in SCI patients, predominantly stimulating leg motor areas of cerebral cortex, just as we did in this study. However, the therapeutic parameters of TMS in our proposed protocol were different from those in these two previous reports. For SCI patients, Benito et al. therapeutically applied 20-Hz TMS with an intensity of 90% of MT in the lower limb using a double-cone coil.8 During the study, they provided 1800 pulses per day for 15 days (27,000 pulses in total). In the study by Kumru et al., similarly, 1800 pulses of 20-Hz TMS with a double-cone coil were provided daily for 20 days (36,000 pulses in total).9 They chose 90% of MT in the lower leg as the intensity of stimulation. In our proposed protocol, in contrast, the intensity of TMS was set as 110% of MT, and 3000 pulses of TMS were provided daily for 15 days (45,000 pulses in total). Therefore, the magnetic stimulation

<table>
<thead>
<tr>
<th>ASIA score</th>
<th>At admission</th>
<th>69th day after admission</th>
<th>76th day after admission (First day of TMS)</th>
<th>94th day after admission (Last day of TMS)</th>
<th>At discharge (130th day after admission)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor score (points)</td>
<td>Right</td>
<td>23</td>
<td>28</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>27</td>
<td>34</td>
<td>34</td>
<td>39</td>
</tr>
<tr>
<td>Sensory score (points)</td>
<td>Right</td>
<td>106</td>
<td>112</td>
<td>112</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>106</td>
<td>112</td>
<td>112</td>
<td>112</td>
</tr>
<tr>
<td>Knee extensor muscle strength (N)</td>
<td>Right</td>
<td>124</td>
<td>NA</td>
<td>138</td>
<td>159</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>127</td>
<td>NA</td>
<td>145</td>
<td>159</td>
</tr>
<tr>
<td>Maximum calf circumference (cm)</td>
<td>Right</td>
<td>33.0</td>
<td>NA</td>
<td>32.0</td>
<td>33.5</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>34.0</td>
<td>NA</td>
<td>33.0</td>
<td>34.0</td>
</tr>
<tr>
<td>MAS (Grade)</td>
<td>Right</td>
<td>1+</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>1+</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>SPPB (points)</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ABMS-2 (points)</td>
<td>12</td>
<td>NA</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>FIM (points)</td>
<td>44</td>
<td>NA</td>
<td>59</td>
<td>59</td>
</tr>
</tbody>
</table>

in our protocol can be considered to be more intense and more abundant than those in the previous studies.

The underlying mechanism of functional recovery with TMS in the studied patient still remains to be investigated. According to the report by Ziemann et al., TMS application can increase cortical drive originating from cerebral cortex in humans. In addition, some researchers have reported that the increase of cortical drive to surviving corticospinal neurons can lead to motor functional recovery in SCI patients. Therefore, we speculate that 10-Hz TMS applied in SCI patients could increase motor cortical excitability and subsequently enhance descending corticospinal projections in the spinal cord, which is likely a core mechanism for the observed functional recovery. Regarding the intensity of magnetic stimulation, we expected that higher intensity and more abundant magnetic stimulation would produce more enhancement of spinal longitudinal neurons and would stimulate cortical motor areas more broadly to cover not only areas for leg movement but also those for hand movement. However, for stroke patients, TMS application with an intensity of greater than or equal to 120% of MT in the limb has been rarely reported. Therefore, we decided to apply magnetic stimulation of 110% for the studied SCI patient abundantly for 15 days. From the results of this case study, the safety and feasibility of our proposed protocol with TMS of 110% intensity proved to be acceptable. However, the optimal intensity and total amount of stimulation applied in therapeutic protocols for SCI patients should be determined in further studies.

The selection of stimulating coil seems to be a critical issue when TMS is applied as a therapeutic tool for SCI patients with tetraparesis. TMS with a double-cone coil as applied in our protocol reportedly produces a deeper and more extensive magnetic field over the cerebral cortex than TMS with a usual circular coil. In our patient, apparent movements of bilateral upper limbs were evident when TMS was applied over the midsagittal plane, indicating that bilateral hand motor areas were effectively stimulated as well as bilateral leg motor areas. We can expect that motor functional recovery would be facilitated not only in lower limbs but also in upper limbs with this TMS application using a double-cone coil. Therefore, it is recommended that a double-cone coil be used therapeutically for such tetraparetic SCI patients.

We provided rehabilitative training combined with TMS application as Benito et al. and Kumru et al. did in their protocol. In their protocols, gait training was mainly provided. In contrast, because of the severity of the neurological symptoms, physical training other than gait training was mainly provided for our patient. Taking the results of the previous two studies into account, it is strongly recommended that rehabilitative training be combined with TMS application simultaneously for SCI patients. However, the program of

Fig. 2. Application of TMS with a double-cone coil
rehabilitative training for SCI patients receiving TMS should be based on the severity of motor disturbance.

There are some limitations in this case study. First, the efficacy of our proposed protocol featuring TMS with an intensity of 110% for a patient with SCI should be confirmed in a randomized controlled study with control subjects. Second, the optimal latency between the injury and application of TMS needs to be determined. Earlier introduction of the protocol with TMS might have produced a better improvement of motor function in the affected limbs. Third, no neurophysiological study, such as the measurement of motor evoked potentials, was performed to investigate motor neuron excitability. As mentioned above, the introduction of TMS combined with rehabilitative training might have influenced the cortical excitability. The relationship between neurophysiological change and functional recovery with the studied intervention should be investigated in the future.

CONCLUSION

This case study demonstrated the safety and feasibility of TMS combined with rehabilitative training in a patient with incomplete SCI. The proposed combined protocol featuring the application of TMS with relatively high stimulation intensity might be a novel neurorehabilitation intervention for such a patient, although the appropriateness of this protocol needs to be confirmed in a larger number of patients.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES


