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The Effect of High Frequency Repetitive Transcranial Magnetic Stimulation on Community Ambulation Ability in Spinal Cord Injury Patients: A Randomized Controlled Trial

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This study was conducted to investigate the effects of high frequency repetitive transcranial magnetic stimulation (rTMS) on spasticity and gait ability in incomplete spinal cord injury (SCI) patients. 14 subjects were randomly assigned to each of 7 experimental and control groups. 20 Hz high frequency rTMS was applied to the experimental group for 20 minutes per day, 5 times a week for a total of 4 weeks and sham rTMS was applied to the control group. The subjects were assessed for spasticity by Modified Ashworth Scale (MAS) and Spinal Cord Injury Assessment Tool for Spasticity (SCATS). In the evaluation of gait ability, 10 Meter Walk Test (10MWT) for gait speed and Community walk test (CWT) for ability of community ambulation were used. A significant improvement in MAS, SCATS, 10MWT and CWT was observed after intervention in the experimental group ($p < 0.05$), and there was a significant improvement in all evaluation items compared to the control group ($p < 0.05$). The results of this study suggest that high frequency rTMS applied to primary motor cortex (M1) positively affects spasticity and gait ability in incomplete spinal cord injury patients.

Keywords : spasticity, community ambulation, gait, high frequency repetitive transcranial magnetic stimulation, magnetic field, spinal cord injury

1. Introduction

Spinal cord injury (SCI) is a disease that causes serious disability, affecting approximately 40 million people worldwide and 2.1 to 130.7 million in developing countries each year [1]. Patients with SCI have impaired sensory and motor functions that affect activities of daily living and physical functions, and more than 60 % of them have spasticity [2].

Spasticity is a representative symptom of various central nervous system lesions (such as stroke, spinal cord injury and cerebral palsy), namely, upper motor neuron (UMN) syndrome. Spasticity is defined as a velocity-dependent increase in the tonic stretch reflex (muscle tone), and occurs due to lesions of the pyramidal and extracorporeal pathways [3]. Spasticity negatively affects daily living activities and self-management abilities, thereby reducing the quality of life. In addition, if there is spasticity, the risk of developing bedsores due to movement problems increases, and patients with severe spasticity become bedridden [4]. The main cause of spasticity after SCI is damage to the descending corticospinal pathways, which is responsible for regulating spinal segments. In addition, it was demonstrated that patients with spasticity showed decreased excitability of the disynaptic reciprocal inhibitory pathway [5]. The interneurons in the disynaptic reciprocal inhibitory pathway are activated by supraspinal commands before and at the onset of agonist contraction. In patients with spinal cord injury, this mechanism is impaired, and the supraspinal control of interneurons in the disynaptic reciprocal inhibitory pathway is reduced, resulting in spasticity [6].

In patients with incomplete SCI, gait is one of the most affected of daily living activities. In American Spinal Injury Association Impairment Scale (AIS), which is most often used to evaluate the severity of SCI, C and D grades are cases where walking is possible with various walking aids, but it requires considerable energy, and there are many disorders to outdoor walking represented by community walking [7]. In patients with incomplete SCI, the

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quality and ability of gait are affected by weakness of lower extremity muscle strength or sequencing disorder of muscle activation, but another factor that is significantly affected is spasticity [8].

SCI is a lesion that leaves many physical disorders, and various types of stem cells and regeneration-related gene studies are being conducted to regenerate neurons damaged by SCI [9, 10]. However, these methods are invasive, and there are several controversies regarding stability. Another treatment strategy for functional restoration after SCI is to improve neuroplasticity, but neuroplasticity after SCI has not been studied as much as after brain lesions. However, since several studies have reported collateral sprouting of spared axons to disconnected tracts and cortical remapping in incomplete SCI animal models, functional recovery through plasticity can be expected [11].

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation based on the principle of electromagnetic induction and is used as an intervention method for motor disorder or spasticity caused by lesions of the brain or spinal cord. rTMS induces membrane depolarization and action potential by forming a magnetic field that induces a potential difference across the neuronal membrane by the current passing through the coil located on the head surface. Spasticity is caused by a decrease in inhibitory upper-motor neuron activity, which leads to over-activation of α and γ motor neurons and interneurons at the level of the spinal cord. rTMS is used as an intervention to modulate the excitability of upper motor neurons [12].

According to a previous study, it was reported that the application of high frequency rTMS to the primary motor cortex of patients with spastic quadriplegia or cerebral palsy reduced H-reflex size and spasticity [13]. Benito *et al.* investigated the effect of high frequency rTMS in 17 patients with incomplete SCI. As a result, it showed a significant improvement in the motor function evaluated by AIS, and the significant effect in the gait function evaluated by 10MWT and TUG test lasted for 2 weeks. It also showed a significant improvement in spasticity evaluated by MAS [14]. Centonze *et al.* reported that 5Hz rTMS applied to the primary motor cortex of the legs of patients with multiple sclerosis improved lower limb spasticity, and showed that there was continuous improvement in lower limb spasticity even after 2 weeks of intervention [6].

However, although there are previous studies showing that rTMS has a significant effect on the spasticity of patients with neurological disorders, there are few studies on patients with incomplete SCI, and few studies have evaluated spasticity and gait ability together.

Therefore, the purpose of this study was to investigate the effect of high frequency rTMS on spasticity and gait ability in patients with incomplete SCI.

2. Materials and Methods

2.1. Participants

This study was conducted in 14 patients with SCI who are admitted to a rehabilitation hospital.

The inclusion criteria for selection are as follows: (1) incomplete SCI by trauma on the American Spinal Injury Association Disability Scale (AIS) D grade, (2) cervical or thoracic SCI, (3) spasticity affecting lower limbs with a Modified Ashworth Scale (MAS) > 1+ (4) more than 6 months after SCI, (5) Mini-Mental State Examination (MMSE-K) score of 21 points or more (understanding of the instructions), and Walking is an anti-gravity activity, so muscle strength of F grade (full range of motion against gravity) or higher is required in the manual muscle test. The reason why patients with AIS D in the inclusion criteria of this study is that the muscle whose grade D is paralyzed indicates muscle strength of F or higher.

The exclusion criteria for selection are as follows: (1) history of brain-related diseases (e.g., stroke), (2) orthopedic problems (e.g., joint contracture or fracture), (3) history of seizure, and (4) device inserted into the heart or brain.

Informed consent was obtained from all patients according to the ethical standards of the Declaration of Helsinki.

2.2. Study design

After the initial evaluation, subjects were randomly assigned to experimental groups (n = 7) or control groups (n = 7). Card flip was used for randomization. Each card was marked with 0 or 1, and subjects who choose a card marked with 0 were assigned to the experimental group. All subjects were blinded to their group until the study was completed. Two clinicians were involved in the study, randomization of group and application of rTMS were performed by clinician 1. And pre- and post-treatment assessments were performed by clinicians 2 blinded to group assignment.

The experimental group received real rTMS and rehabilitation therapy as an intervention, and the control group received sham rTMS and rehabilitation therapy. The subjects received real or sham rTMS before rehabilitation therapy. The rTMS intervention was conducted for 20 minutes at a time, five times a week for 4 weeks.

Fig. 1. (Color online) The repetitive transcranial magnetic stimulation device.

2.3. Intervention

2.3.1. Repetitive transcranial magnetic stimulation (rTMS)

Participants received rTMS using Magstim Rapid2 (Magstim Co Ltd, Wales, United Kingdom) connected with figure-eight-shaped coil, and this was held over the primary motor cortex (M1) (see Fig. 1). The rTMS was applied based on the vertex position of the International 10-20 EEG system to stimulate the bilateral lower limb motor area. For real rTMS, we applied 2-s-long bursts at 20 Hz with inter-stimulus interval of 28 s, for a total of 1600 pulses over 20 min. The coil for sham rTMS was applied to the scalp at an angle of 90 degrees so that subjects could hear the sound of the machine operating, but the electric current was not induced in the brain.

Resting motor threshold (RMT) was defined as the minimum stimulation intensity of TMS needed to elicit 50 % or more within 10 trials electromyographic responses ≥ 50 μV on the right biceps brachii muscle [15]. In this study, the intensity was set to 90 % of the individual's RMT.

All participants received rTMS before rehabilitation therapy using the same equipment during the same time of day.

2.4. Outcome measure

In this study, spasticity was assessed by the Modified Ashworth Scale (MAS) and the Spinal Cord Injury Assessment Tool for Spasticity (SCATS). And the subjects' gait ability was assessed by the 10 m walk test (10MWT) and the community walk test (CWT). All measurements were performed before rTMS intervention and after rTMS intervention for 4weeks.

2.4.1. Modified Ashworth Scale (MAS)

MAS is available in its original form devised by Ashworth in 1964 and was modified by Bohannen and Smith in 1987. The examiner moves the subject's limbs through the entire range of motion, and the amount of resistance felt at that time is indicated by a number corresponding to 0 to 4 described on the scale (Table 1) [16]. In this study, to determine the effect of the excitability control of the motor cortex through rTMS on the spasticity of the lower extremities in SCI patients, the knees of the subjects were examined as in previous study [15].

2.4.2. Spinal Cord Injury Assessment Tool for Spasticity (SCATS)

SCATS was developed for the clinical measurement of spastic hypertonia and consists of measurements of clonus, flexor, and extensor spasms. In this study, extensor spasms were measured. The measurement method was to place the knee and hip on the examination side at a bending angle of 90 to 110 degrees while the other leg was extended, and then the two joints were simultaneously extended. When the response was induced, the muscle contraction time seen in the quadriceps muscle was measured and recorded [17].

2.4.3. 10 Meter Walk Test (10MWT)

10MWT is a widely used evaluation tool to evaluate gait speed. Subjects are required to walk a total of 14 meters, measuring middle 10 meters of time taken to walk

Table 1. Modified Ashworth Scale (MAS).

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimum resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a slight catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement
2	More marked increase in muscle tone through most of the range of movement, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

excluding the first 2 meters and the last 2 meters, corresponding to the acceleration and deceleration sections. In this study, three measurements were repeated with a 2-minute inter-rest, and the average was used as data. The intra-measurement reliability of 10MWT is r = .88, and the inter-measurement reliability is r = .99 [18].

2.4.4. Community walk test (CWT)

CWT was performed to evaluate community ambulation ability, and the time taken to walk 300 m at a comfortable pace in the community near the hospital where the subjects were admitted was measured using a stopwatch. After that, the coefficient was multiplied according to the level of the walking aid used by the subjects. The coefficients for each level of walking aids are as follows : no aid, ×1; ankle foot orthosis, ×2; mono cane, ×3; quadruped cane, ×4; ankle foot orthosis and mono cane, ×5; and ankle foot orthosis and quadruped cane, ×6 [19].

Differences in general characteristics between the experimental group and the control group before intervention were compared using the Mann-Whitney tests and chi-square tests. The Wilcoxon signed-rank tests were performed to assess the before and after effects in each group. The Mann-Whitney tests were used to assess differences between real rTMS and sham rTMS. For all analyses, p values < 0.05 were considered significant. Data were expressed as the mean ± standard deviation (SD) and statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Table 3. Comparison of change in characteristics of the experimental group and control group. When there was a statistically significant difference using Wilcoxon signed-rank and Mann-Whitney tests, symbols * and † were used to indicate.

	EG (n = 7)	CG (n = 7)	z	p
MAS of right knee (grade)				
Pre-test	2.90 ± 0.48	2.84 ± 0.43	-0.32	0.74
Post-test	2.26 ± 0.19	2.73 ± 0.49	-1.94	0.05
z	-2.21	-0.16		
p	0.03*	0.86		
MAS of left knee (grade)				
Pre-test	3.00 ± 0.66	2.96 ± 0.65	-0.25	0.79
Post-test	2.29 ± 0.23	2.86 ± 0.54	-2.25	0.02†
z	-2.12	-0.95		
p	0.03*	0.34		
SCATS (score)				
Pre-test	6.04 ± 0.44	5.91 ± 0.43	-0.38	0.70
Post-test	4.60 ± 0.14	5.20 ± 0.58	-2.24	0.02†
z	-2.37	-2.36		
p	0.01*	0.01*		
10MWT (m/s)				
Pre-test	0.51 ± 0.08	0.57 ± 0.11		
Post-test	0.89 ± 0.05	0.62 ± 0.17		
z	-2.37	-0.16	-1.54	0.12
p	0.01*	0.86	-2.23	0.02†
CWT (min)				
Pre-test	54 ± 4.08	53.71 ± 4.92		
Post-test	32.57 ± 6.77	46.43 ± 9.64		
z	-2.37	-2.11	0.00	-3.60
p	0.01*	0.03*	1.00	0.00†

3. Results and Discussions

The general characteristics of the subjects are summarized in Table 2, and there were no statistically significant differences in the characteristics of the subjects between the two groups.

In this study, the evaluation of the subject's spasticity was performed through MAS and SCATS, and the evaluation of gait ability was performed using 10MWT for gait speed and CWT for ability of community ambulation. The values of MAS, SCATS, 10MWT and CWT in the experimental and control groups are summarized in Table 3. The results of this study, there was a significant difference between before and after intervention in MAS, SCATS, 10MWT and CWT in the experimental group ($p < 0.05$). And there was significant difference between groups in all variances ($p < 0.05$) (see Fig. 2, 3, 4, 5).

The results of MAS and SCATS, which are evaluations of spasticity, showed significant improvement in the

Table 2. General and medical characteristics of subjects. There was no statistically significant difference between the two groups as a result of using Mann-Whitney and chi-square tests.

	EG (n = 7)	CG (n = 7)
Age (years)	45.5 ± 10.24[a]	50.5 ± 10.26
Sex (male/female)	2/5	1/6
Time since SCI (months)	4 ± 2.53	5 ± 1.38
Aetiology (disc prolapse/fracture)	3/4	2/5
Level of lesion (C5/C6/T4/T5/T1/T2/T11/T12)	2/1/1/1/0/1/1	1/0/0/1/2/1/2

[a]Mean ± SD, EG: rTMS, CG: sham Therapy

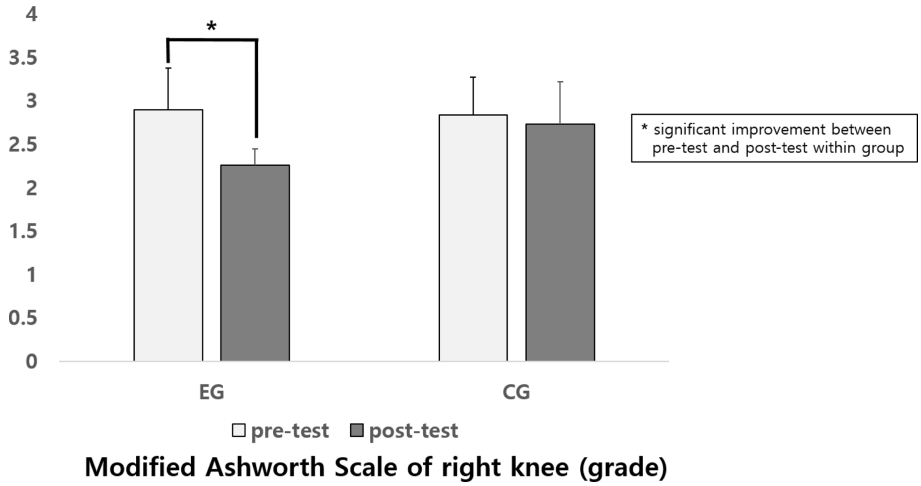

Fig. 2. Comparison of change in MAS of the experimental group and control group. When there was a statistically significant difference, symbols * and † were used to indicate.

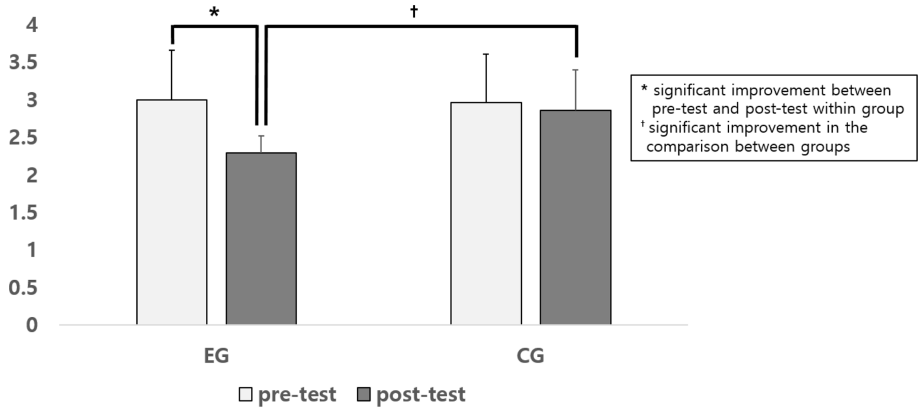

Fig. 3. Comparison of change in SCATS of the experimental group and control group. When there was a statistically significant difference, symbols * and † were used to indicate.

experimental group using rTMS. Kumru *et al.* applied high frequency rTMS to the M1 of 15 patients with incomplete SCI, and showed significant improvement in leg spasticity assessed by MAS, visual analog scale of subjective spastic sensation, Modified Penn Spasm Frequency Scale and Spinal Cord Assessment Tool for Spasticity [15]. These results are consistent with the results of this study. In addition, those authors reported that the effect of reducing spasticity lasted for at least 1 week after 5-day stimulation. As such, the long lasting effect of stimulation seen after the application of rTMS is related to long-term depression. Although a follow-up test was not performed to determine the sustained effects of stimulation in this study, it is considered that the magnitude and duration of such after effects depend on the total number of stimuli, and the longer the application period of rTMS, the more sustained effects of cortical spinal excitability can be induced [20].

High frequency rTMS can increase local glucose metabolism, suggesting a potential increase in stimulated overall neuronal activity [21]. Therefore, it is speculated that rTMS induces improvement of spasticity through reinforcement of descending corticospinal projections.

As a result of this study, as well as spasticity, it was confirmed that rTMS has a significant effect on gait ability. This is believed to be due to the effect of rTMS on plasticity in addition to having a positive effect on exercise performance as spasticity improved. In previous studies that applied high frequency rTMS to various neurological diseases, it was reported that walking ability was improved. Lomarev *et al.* reported improvement in gait speed in patients with brain injury, and Nuara *et al.* reported improvement in gait ability in patients with multiple sclerosis [22, 23].

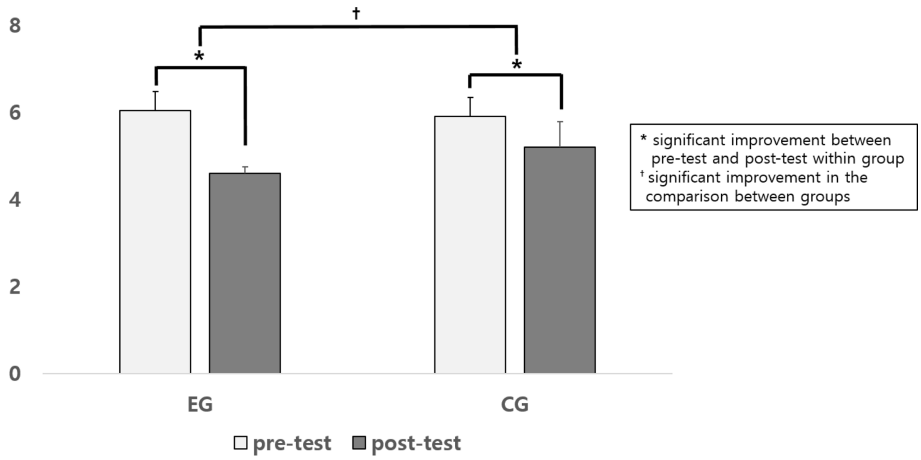

Fig. 4. Comparison of change in 10MWT of the experimental group and control group. When there was a statistically significant difference, symbols * and † were used to indicate.

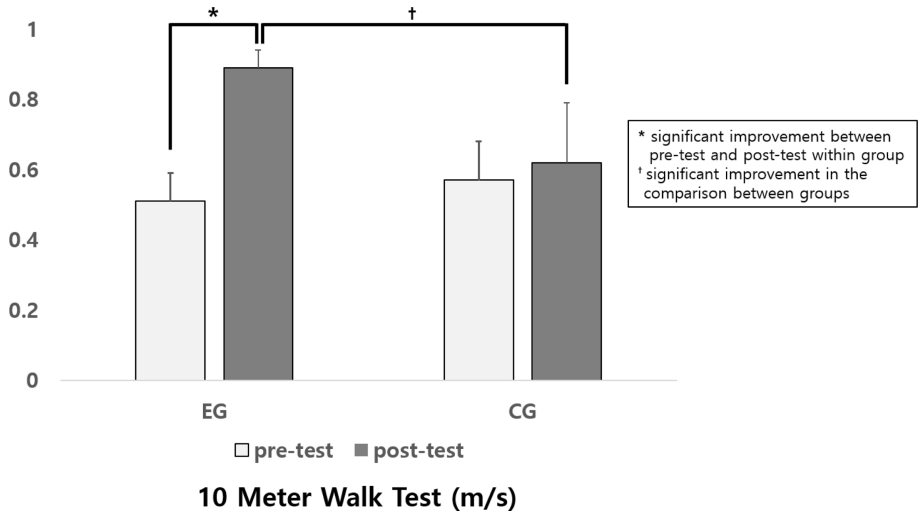

Fig. 5. Comparison of change in CWT of the experimental group and control group. When there was a statistically significant difference, symbols * and † were used to indicate.

There are several mechanisms that show various effects when rTMS is applied to neurological disorders: neurotrophic effects through regulation of secretion of brain-derived neurotrophic factor (BDNF) and glutamate, synaptic plasticity through long-term potentiation and long-term depression, anti-apoptotic effects, and magnetic-field-induced bio-physiological effects [24].

Especially, rTMS rebuilds neural circuits through synaptic plasticity through enhancement of BDNF-tropomycin receptor kinase B (BDNF-TrkB) complex signaling and upregulation of the N-methyl-D-aspartate (NMDA) receptors [25]. It was confirmed that this remodeling leads to a change in connectivity within the brain through the results of research using functional magnetic resonance imaging. Previous study applied high frequency rTMS to M1, reported that the connectivity between M1 and other brain regions was reduced. It is believed that this decrease in connectivity with other brain regions improves the descent output of the motor cortex and improves the function of the pyramidal tract [26].

In addition, rTMS can increase or decrease brain activity. High frequency rTMS increases the corticospinal and M1 excitability, whereas low frequency rTMS decreases them, which can change the excitability of the spinal neuronal circuits. Therefore, it is possible to improve the sensory and motor functions of SCI patients through the application of rTMS [27, 28].

As a result of this study, the gait speed and ability of

community ambulation were improved after the application of rTMS. In particular, 10MWT of the experimental group increased to 0.8 m/s after rTMS intervention, which means that outdoor walking is possible. When interpreting the results of 10MWT clinically, it is considered that less than 0.4 m/s is for indoor walking, 0.4 to 0.8 m/s is for indoor and limited outdoor walking, and more than 0.8 m/s is for outdoor walking [18]. Therefore, 10MWT is a test for gait speed, but when looking at the interpretation of these 10MWT results, it is considered that the improvement in gait speed is closely related to the improvement in community ambulation ability represented by outdoor walking ability.

This study has some limitations. First, since the sample size was small and only SCI patients who met the set criteria were targeted, it cannot be generalized to all SCI patients. Second, there was the absence of follow-up to investigate the persistence effect of rTMS. Future studies can be used as an effective guideline for the application of rTMS to SCI patients, provided that the presence or absence of a sustained effect and the factors affecting the sustained effect are evaluated together.

4. Conclusion

This study was conducted to investigate the effects of 20Hz high frequency rTMS applied to M1 of patients with SCI on spasticity, gait speed, and ability of community ambulation. The spasticity that more than half of SCI patients have, by itself, causes problems such as pain or muscle spasms, but secondarily, due to problems related to movement, it brings a great limit to walking or daily activities. Based on the results of this study, we propose that applying high frequency rTMS to the M1 region of SCI patients is effective intervention for improvement of spasticity and gait ability.

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