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Case report

Repetitive transcranial magnetic stimulation accuracy as a spinal cord stimulation outcome predictor in patients with neuropathic pain

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ABSTRACT

Object: Spinal cord stimulation (SCS) is an effective albeit invasive and relatively expensive treatment of neuropathic pain. Repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex (M1) is a non-invasive treatment of neuropathic pain. The aim of the current study was to investigate whether rTMS can predict the successful outcome of SCS.

Methods: The study population consisted of 22 patients with neuropathic pain who had undergone SCS and rTMS. We conducted statistical analyses to identify the factors that predict pain reduction following SCS.

Results: Multiple regression analyses showed that only degree of pain relief following rTMS was statistically correlated with success in SCS; on the other hand, age, sex, lesion location, pain duration and laterality, and targeted extremities were not correlated. Using receiver-operating characteristic (ROC) curve analyses of the pain relief following rTMS, the diagnostic sensitivity for successful SCS was 0.60 and the specificity was 0.83.

Conclusions: The degree of pain relief following rTMS over M1 is a significant prognostic factor of SCS outcome in patients with intractable neuropathic pain.

Significance: The current study provides evidence showing that rTMS, a non-invasive and relatively easy to administer procedure, may aid in the selection of suitable candidates for SCS treatment.

1. Introduction

Since Shealy et al. reported pain relief following electrical stimulation of the dorsal spinal cord, spinal cord stimulation (SCS) has been applied to various types of chronic neuropathic pain that are refractory to ordinary medical treatments, including medication and physical therapy [5,16,17,26]. However, SCS requires invasive procedures, insertion of electrodes, and implantation of a pulse generator, which can cause complications such as injury of nerve or vessels, infection or dysfunction of devices requiring reoperation, cerebrospinal fluid leak, and SCS-related pain [15]. In addition, SCS is not always effective for neuropathic pain, and so test stimulation using an external stimulator for approximately one week (SCS trial) is performed before permanent implantation of the devices. Pain relief by test stimulation is well correlated with the outcome of SCS after permanent implantation of devices, but the SCS trial also requires invasive procedures that can cause similar complications as SCS permanent implantation. Several studies aiming to identify the predictors of SCS success have been conducted [7,32], but no study has thus far reported the prognostic

Abbreviations: ACC, anterior cingulate cortex; AUC, area under the curve; CPSP, central post-stroke pain; DMN, default mode network; EMCS, electrical motor cortex stimulation; FBSS, failed back surgery syndrome; fMRI, functional magnetic resonance imaging; RMT, resting motor threshold; ROC, receiver operating characteristic; PET, positron emission tomography; rTMS, repetitive transcranial magnetic stimulation; SCS, spinal cord stimulation; VAS, visual analogue scale.

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accuracy of other treatments for neuropathic pain, such as repetitive transcranial magnetic stimulation (rTMS).

High-frequency rTMS to the primary motor cortex is known to be a non-invasive treatment for neuropathic pain. First, the pain relief achieved by electrical motor cortex stimulation (EMCS) was reported in 1993 and several studies have since reported favorable outcomes [25,31]. However, EMCS requires invasive procedures, including craniotomy and implantation of intracranial electrodes and a pulse generator. Then, rTMS has been investigated as a non-invasive predictor of the outcome of EMCS [11,20,25]. Since a significant correlation between pain relief by rTMS and EMCS was found, rTMS has come to be accepted as a non-invasive treatment for neuropathic pain [2,10,12,19,22,24].

The neurobiological mechanisms of pain relief by SCS and rTMS are not completely understood. Several studies have indicated that supraspinal modulation of neuronal activity plays an important role in relieving the neuropathic pain by SCS [3,23]. Recently, several neuroimaging studies have reported that the change of brain activity is correlated to pain relief produced by SCS [6,9,13]. It should be noted that many of the brain regions reported in those studies are known to be involved in pain relief by rTMS over M1 [18]. Therefore, we assumed that the similar mechanisms are involved in neuropathic pain relief produced by SCS and rTMS over M1, and retrospectively investigated a correlation between the outcome of SCS and that of rTMS over M1 in patients with neuropathic pain.

2. Materials and methods

2.1. Patients

The current study population consisted of 22 patients with intractable neuropathic pain who were delivered rTMS in our clinical study [12,29] and underwent SCS at the Osaka University Hospital (Table 1) from April 2005 to February 2015. All patients had been refractory to ordinary medical treatments for more than six months and met the diagnostic criteria for neuropathic pain based on the precise grading system developed by Treede et al. [30]. The patients who participated the randomized, double-blind rTMS studies were routinely proposed SCS trial as one of the treatment options covered by medical insurance. The sample consisted of 13 men and 9 women. The average age was 63 (SD = 8.83, range = 50–79) years. The intractable neuropathic pain was caused by central post-stroke pain (CPSP) in 19 patients (hemorrhage in 15 and infarction in four), failed back surgery syndrome (FBSS) in two, and subacute combined degeneration of the spinal cord in one. Nine patients had stroke lesions on their putamen and seven patients had stroke lesions on their thalamus. Pain was left-sided in 11 patients, right-sided in eight patients, and bilateral in three patients. In cases where patients had bilateral pain, the side having stronger pain was targeted by rTMS (left in two and right in one). The target of stimulation was the upper limb in five patients and the lower limb in 17 patients. It means that the lead was placed at the level of cervical spine in five patients and lower thoracic spine in 17 patients. The mean duration of the disease was 52.8 (SD = 42.8, range = 6–168) months.

Exclusion criteria were dementia (Mini Mental Status Examination <24), higher brain dysfunction, and major depression.

2.2. Pain evaluation

All patients underwent an SCS puncture trial and pain intensity was scored a few days before and one week after operation using the visual analogue scale (VAS). If the SCS trial achieved more than 30% pain reduction, patients were considered to be "responders to SCS" by referring to the previous study [1]. All patients also underwent rTMS over M1 and recorded the VAS just before and after rTMS to evaluate pain intensity. The results of rTMS were extracted from our previous studies [12,29].

Table 1
The characteristics of patients.

Patient	Gender	Age	Targeted side	Targeted limb	Underlying diseases	Location of lesion	Pain duration (months)	ΔVAS after figure-8 rTMS (%)	ΔVAS after SCS trial (%)	Good outcome one year after SCS implant
1	M	63	Left	Lower	FBSS	Lumber vertebra	36	6.76	41.6	YES
2	M	51	Right	Lower	FBSS	Lumber vertebra	42	18.1	37.5	YES
3	M	60	Left	Lower	CPSP	Thalamus	24	12.5	18.75	–
4	F	70	Right	Lower	CPSP	Putamen	22	8.54	50	YES
5	F	55	Left	Lower	SCD	Spinal cord	81	-6.94	0	–
6	F	72	Left	Lower	CPSP	Putamen	168	12.5	30	YES
7	M	66	Right	Lower	CPSP	Putamen	24	0	0	–
8	M	75	Left	Lower	CPSP	Putamen	156	16	0	NO
9	M	50	Right	Lower	CPSP	Putamen	32	-1.39	0	–
10	F	75	Right	Upper	CPSP	Thalamus	25	75	57.1	–
11	M	51	Left	Lower	CPSP	Putamen	21	65.8	65.1	–
12	F	62	Left	Lower	CPSP	Subcortical	7	53.6	25	–
13	F	51	Left	Lower	CPSP	Thalamus	48	14.2	57.1	YES
14	F	63	Left	Lower	CPSP	Medulla oblongata	47	1.3	10.5	–
15	M	56	Left	Lower	CPSP	Thalamus	6	5.9	35.9	–
16	M	75	Right	Upper	CPSP	Thalamus	102	36.8	37.5	–
17	F	67	Left	Upper	CPSP	Putamen	36	4.65	0.0	NO
18	M	63	Right	Lower	CPSP	Putamen	91	0	0	–
19	M	70	Right	Upper	CPSP	Thalamus	39	-8	0	NO
20	F	57	Left	Lower	CPSP	Putamen	84	12.8	16.7	–
21	M	55	Right	Lower	CPSP	Subcortical	30	0	0	–
22	M	79	Left	Upper	CPSP	Thalamus	40	28.1	31.3	YES
Mean (SD)		63 (8.8)					52.8 (42.8)	16.2 (22.1)	23.4 (21.7)	

VAS, visual analogue scale; FBSS, failed back surgery syndrome; CPSP, central post-stroke pain; SCD, subacute combined degeneration of spinal cord.

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