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Electrical or repetitive transcranial magnetic stimulation of primary motor cortex for intractable neuropathic pain

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Abstract— Objective: To assess the pain-relieving effects of motor cortex electrical stimulation (MCS) and the predictive factors retrospectively.
Methods: Thirty-four patients with intractable neuropathic pain underwent MCS; 19 patients had cerebral lesions, and 15 had non-cerebral lesions. In selected 12 patients, test electrodes were implanted within the central sulcus and on the precentral gyrus. Twelve patients received both MCS and repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex.
Results: Pain reduction of >50% was observed in 12 of 32 (36%) patients with >12 months follow-ups (2 patients were excluded because of short follow-up). In 10 of the 12 patients who received test electrodes within the central sulcus and on the precentral gyrus, the optimal stimulation was MCS within the central sulcus. In 4 of these (40%) patients, positive effects were maintained at follow-ups. The pain reduction of rTMS significantly correlated with that of MCS during test stimulation.
Conclusions: The test stimulation within the central sulcus was more effective than that of the precentral gyrus. In the selected patients, chronic stimulation within the central sulcus did not significantly improve long-term results. Repeated rTMS seems to be same effective as MCS.

I. Introduction

Neuropathic pain is very difficult to treat and is usually refractory to medical treatment. In 1991, Tsubokawa et al reported that post-stroke pain can be reduced by motor cortex stimulation (MCS)[1]. Other types of neuropathic pain (phantom-limb pain, pain due to brachial plexus avulsion or spinal cord injury and complex regional pain syndrome type II) also respond well to MCS [2]. MCS is effective in 50–75% of patients with these types of intractable neuropathic pain [2].

In most of the early studies on MCS, the electrodes were implanted epidurally via a burr hole. Such an epidural method might not provide optimal pain relief because both the method and the area subjected to test stimulation are restricted by the brief operative period and the single burr hole. The main portion of the primary motor cortex (M1), particularly the area corresponding to the hand, is located within the central sulcus, and only a small portion of M1 appears on the precentral gyrus.

Therefore, we modified the epidural method to a subdural method and incorporated implantation within the central sulcus. These modified methods are applied to the patients with neuropathic pain who had severe motor dysfunction, because dissection of the central sulcus may develop new motor deficit. We already reported the preliminary results [3].

Recently, repetitive transcranial magnetic stimulation (rTMS) of M1 has been applied in the treatment of neuropathic pain [4,5]. In a few studies, a correlation between the efficacy of rTMS and that of MCS was reported, and it was suggested that rTMS had the potential to predict the efficacy of MCS [6].

In this retrospective and exploratory study, we report the results, including long-term follow-up, obtained with our modified method with subdural electrodes placed on the precentral gyrus or within the central sulcus, in a consecutive series of 34 patients with intractable neuropathic pain. The exploratory analyses of the relations between MCS efficacy and several clinical factors, including underlying disease and the pain reduction of rTMS of M1, are reported.

II. Methods

Subjects

Subjects comprised consecutive 34 patients (28 men, 6 women; mean age, 57.0 years; range, 28–76 years) suffering from intractable neuropathic pain. The mean history of pain was 5.4 years (range, 0.5–28 years). Eighteen patients had post-stroke pain; strokes were due to thalamic hemorrhage or infarction (n=11), putaminal hemorrhage (n=3), brainstem hemorrhage or infarction (n=3), or temporoparietal subcortical infarction (n=1). One patient had pain related to pontine injury. Other origins of pain included brachial plexus avulsion (n=7), phantom-limb pain (all of lower limbs; n=4), spinal cord lesion (n=2), trigeminal neuropathic pain (n=1) and peripheral nerve injury (n=1). Patients were assigned to 1 of 2 groups according to the type of

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lesion: cerebral lesion group (15 men, 4 women; mean age, 61.1 years; range, 50–76 years) or non-cerebral lesion group (13 men, 2 women; mean age, 51.8 years; range, 28–74 years). Pain topography was localized on the right side in 14 patients, on the left side in 18 patients and bilaterally in 2 patients and concerned the entire half body in 2 patients, the face and upper limb in 2 patients, the upper limb and lower limb in 4 patients, the face in 2 patients, the upper limb in 14 patients and the lower limb in 10 patients. Twenty-nine of these patients were partly reported [3,6].

Eleven patients (10 men, 1 woman; mean age, 52.8 years; range, 28–74 years) underwent both rTMS and MCS. Of these, 5 had post-stroke pain; strokes were due to thalamic hemorrhage or infarction (n=2), putaminal hemorrhage (n=2) or brainstem infarction (n=1). Other origins of pain included phantom-limb pain (n=2), brachial plexus avulsion (n=1), spinal cord lesion (n=1), trigeminal neuropathic pain (n=1) and peripheral nerve injury (n=1). All patients treated with MCS underwent previous rTMS at Osaka University Hospital. Three of these patients were reported previously [5].

This study was approved by the Ethics Committee of Osaka University Hospital, and written informed consent was obtained from all patients participating in this study.

The surgical procedures used in this study were similar to those reported previously [3,6].

B. rTMS

rTMS was applied through a navigation-guided figure-8 coil (MC B-70, Medtronic Functional Diagnosis A/S, Skovlunde, Denmark) which was connected to a MagPro magnetic stimulator (Medtronic Functional Diagnosis A/S), more than 2 weeks before MCS in 11 patients. First, the resting motor threshold based on the electromyography in the affected muscle area was determined by stimulation of the corresponding M1 area. Muscle twitches in painful areas can be elicited, if stimulated carefully according to the somatotopy. This is possible even with trigeminal lesion and lower limbs. For the patients in whom muscle twitches in the painful areas were difficult to elicit due to severe damage of motor pathways, rTMS was applied with an intensity at 100 A/ls. In our study, 100 A/ls was the maximum tolerable intensity for most patients, with higher intensities resulting in scalp pain [5]. An intensity of 90% of the resting motor threshold was used for treatment. Ten trains of 10-s 5-Hz TMS pulses, with a 50-s intertrain interval, were applied to the M1 area corresponding to the painful area. Thus, a total of 500 stimulations were applied. This protocol is in compliance with the guidelines for the safe use of rTMS [7]. The TMS coil was held and positioned by an articulated coil holder. The Brainsight™ Frameless Navigation system (Rogue Research Inc., Montreal, Canada) was used to monitor the position and direction of the coil, and the position of the patient's head, as described previously [5].

C. Statistical analysis

We evaluated the effectiveness of stimulation for each patient according to the reduction of VAS scores (reduction: $[1\text{-}VAS_{post\text{-}stimulation}/VAS_{pre\text{-}stimulation}] \_ 100$). The difference in the positive effect (latest VAS reduction >50%) between the cerebral lesion group and the noncerebral lesion group was analyzed by Fisher's exact test. Comparison of the VAS reduction in response to rTMS and MCS was made by two sided Wilcoxon's signed rank test. Linear relationship between VAS reduction in response to rTMS and MCS was analyzed by simple linear regression. Mann–Whitney test (the number of group = 2) or Kruskal–Wallis test (the number of group >3) was applied to the comparison of VAS reduction in response to MCS and patient characteristics (age, sex, treated painful region, history of pain, presence or absence of cerebral lesions).

III. RESULTS

A. Perioperative results

Twenty-seven of 34 patients showed various degrees of pain control in response to test stimulation. In the other 7 patients, various patterns of stimulation were tried without success. In 28 patients, one or two Resume electrodes were implanted in the optimal location as determined by test stimulation; one patient for whom test stimulation did not result in pain reduction (the mean reduction in VAS scores was 10%), nonetheless desired permanent Resume implants. In 27 patients, various stimulation patterns were evaluated with the use of grid electrodes to determine the optimal point for pain relief. M1 was identified as the optimal site for pain relief in all of these patients. In 12 selected patients, test electrodes were implanted both within the central sulcus and over the precentral gyrus. In 10 of these patients, test stimulation of M1 within the central sulcus was more effective than that on the precentral gyrus, and a Resume electrode was implanted within the central sulcus. To reduce lower limb pain in 9 patients, a Resume electrode was implanted in the interhemispheric fissure. Among the 34 patients, improvement in the VAS score of >50% was observed in 16 patients (47%) at the time of discharge.

Some patients experienced paresthesias of the painful region in response to MCS. The patients for whom stimulation was successful experienced

paresthesias of the painful region. Most of the patients in this study experienced persistent pain before MCS. Two patients complained of both persistent and shooting pain. MCS was only effective against persistent pain.

MCS and rTMS did not make a constant change in SFMPQ scores. In the patients with a high SF-MPQ score of pre-stimulation, the results of VAS and SF-MPQ tended to be similar. In those with a low SF-MPQ score of pre-stimulation, scores changed little, despite the reduction in VAS scores.

B. Postoperative follow-up

Two patients with peripheral neuropathic pain were excluded from the evaluation of latest pain relief because they could not be followed up for >12 months. Effectiveness of MCS, as indicated by improvement in the VAS score of P50%, was maintained in 12 of 32 patients (36%) with follow-up periods of >12 months. The mean follow-up period in patients who used implanted MCS for P12 months was 50.7 months (range, 13–112 months). In 6 patients, the implants, including electrodes and pulse generator, were removed because of insufficient pain relief. Among the 10 patients with electrodes placed within the central sulcus, improvement in the VAS score of P50% was observed in 6 patients (60%) at the time of the test stimulation and in 4 patients (40%) in the follow-up period. A patient due to post-stroke pain showed excellent pain reduction without electrical stimulation just after the electrode was implanted within the central sulcus. This pain relief in response to dissection of the central sulcus was maintained for several months, but the pain gradually returned.

There was no death related to MCS, but two patients developed cerebral hemorrhage during the follow-up period. A patient died, and the other patient remains in a vegetative state.

C. Correlation between MCS effectiveness and clinical factors

In the cerebral lesion group, improvement in the VAS score of P50% was observed in 8 of 19 patients (42%) at the time of the test stimulation and in 5 of 19 patients (26%) during follow-up periods of >12 months. In the non-cerebral lesion group, improvement in the VAS score of P50% was observed in 8 of 15 patients (53%) at the time of the test stimulation and in 7 of 13 patients (54%) during follow-up periods of >12 months. The absolute numbers suggested that MCS was more effective in the non-cerebral lesion group than in the cerebral lesion group. However, this difference did not reach significance (latest VAS reduction >50%; p = 0.15).

No significant differences were observed between improvement in the VAS score and age, sex, presence or absence of cerebral lesion or treated painful region. The history of pain (P5 years or <5 years) contributed to the latest pain reduction value as determined by the reduction of VAS scores (p = 0.013).

D. Correlation between effectiveness of MCS and that of rTMS

Eleven patients underwent preoperative rTMS of M1 (Table 1). Ten showed some pain reduction with MCS and rTMS (mean VAS reductions were 51.6% and 38.6%, respectively, p = 0.019). The effect of

Fig. 1

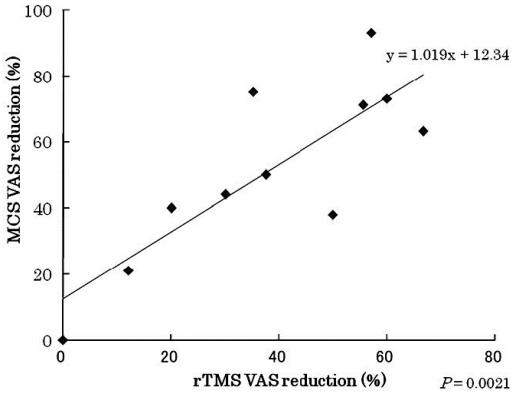

Table 1

Summary of 11 patients who underwent rTMS before MCS

Patient	Age (year)	Sex	Underlying disease	Treated painful region	MCS VAS reduction in test stimulation (%)	rTMS (5 Hz) VAS reduction (%)
C15	71	M	Lt thalamic hemorrhage	Rt upper and lower limb	0	0
N10	28	M	Lt trigeminal pain	Lt face	93	57
C16	62	M	Brainstem infarction	Rt upper limb	63	67
C17	56	M	Rt putaminal hemorrhage	Lt lower limb	73	60
N11	28	M	Spinal cord injury	Rt lower limb	50	38
N12	62	M	Bil phantom-limb pain	Bil lower limb	38	50
N13	57	M	Lt phantom-limb pain	Lt lower limb	44	30
N14	31	M	Lt brachial plexus avulsion	Lt upper limb	71	56
N15	74	F	Rt peripheral nerve injury	Rt lower limb	40	20
C18	55	M	Lt thalamic infarction	Rt upper limb	21	12
C19	57	M	Rt putaminal hemorrhage	Lt lower limb	75	35

M, male; F, female; lt, left; rt, right; bil, bilateral.

rTMS lasted for 3 h after the stimulation in most of patients. Simple linear regression indicated that the pain reduction obtained with rTMS contributed to that obtained with MCS during test stimulation ($p = 0.0021$)(Fig. 1).

IV. Discussion

In this study, MCS was effective in 47% of patients just after implantation and in 36% after a follow-up period of >12 months. Test stimulation of M1 within the central sulcus was more effective than subdural stimulation on the precentral gyrus in 10 of 12 cases. However, chronic stimulation within the central sulcus did not improve long-term results in these selected cases. Neuropathic pain caused by cerebral lesion was suggested to be more refractory to MCS than that caused by non-cerebral lesion, although the difference was not significant. The short-term pain reduction of rTMS correlated well with that of MCS.

Reported predictive factors of MCS efficacy in poststroke pain patients include the absence of severe motor weakness [8], some types of pain, such as trigeminal neuropathic pain [9], and good pain relief with rTMS of M1 [6]. In the present study, pain relief was not associated with patient characteristics (age, sex, presence or absence of cerebral lesion, treated painful region). The latest pain reduction in patients with longer pain duration history (P5 years) was statistically larger than that in the others (<5 years), however, this relationship might be confounded by other variables that were not tested in this study.

The effects of MCS differ according to the lesion causing intractable pain. Post-stroke pain and trigeminal neuropathic pain are both improved significantly by MCS. However, in several reports, trigeminal neuropathic pain appears to respond more favorably than post-stroke pain [2,9]. We recently reported that subthreshold high-frequency rTMS of M1 was more effective in patients with spinal cord or peripheral lesions than in those with cerebral lesions [6]. In the present study, MCS was also suggested to be more effective in patients with non-cerebral lesions than in those with cerebral lesions, although the difference was not significant.

Based on the success of MCS, rTMS is now being applied to intractable neuropathic pain. The detailed patterns and frequencies of MCS and rTMS are different. Usually MCS means monophasic square wave of 30-50Hz and rTMS does biphasic sine wave of 5 or 10Hz. It was reported that high-frequency rTMS (> 1 Hz) of M1 resulted in significant but transient relief of intractable neuropathic pain [4,5]. It has been suggested that results with rTMS may predict the effectiveness of MCS in the treatment of neuropathic pain. In a few recent studies, a correlation between the efficacy of rTMS and that of MCS was reported [4,5]. It's difficult to explain the detailed mechanism of the correlation of efficacies between MCS and rTMS. In the present study, the rate of pain reduction in response to rTMS was significantly correlated with that of MCS over the short term.

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