Effect of Combination Therapy of Low-Frequency Repetitive Transcranial Magnetic Stimulation and Intensive Occupational Therapy on Poststroke Patients with Upper Limb Paralysis

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Abstract

Purpose: We examined the effect of NEURO® (NovEl intervention Using Repetitive TMS and intensive Occupational therapy) on poststroke patients with upper limb paralysis.

Subjects and methods: Subjects were comprised of 95 consecutive patients with a Fugl-Meyer Assessment (FMA) (upper limb portion) score of 46 points or more who received rehabilitation treatment at five centers from April 2015 to March 2017; specifically, 34 patients in the NEURO® group, 27 patients in the chronic phase group and 34 patients in the recovery phase group (46 patients with cerebral infarction, 48 patients with cerebral hemorrhage, and 1 patient with cerebral contusion). Evaluation methods included the FMA for hemiplegia.

Results: FMA scores showed significant improvement in the NEURO® and the recovery phase groups. However, no significant improvement was observed in the chronic phase group. There was no significant difference between the NEURO® and recovery phase groups for the difference in changes to the FMA score.

Conclusion: Similar to the improvement generally observed in the recovery phase, NEURO® was demonstrated to be effective even in the chronic phase if patients indicated for the therapy were adequately selected. Therefore, combination therapy of low-frequency repetitive transcranial magnetic stimulation and intensive occupational therapy for hemiplegic stroke patients is superior to functional improvement for poststroke patients with upper limb paralysis in the chronic phase.

Keywords: Stroke; Occupational therapy; Repeated transcranial magnetic stimulation; Upper limb

Introduction

Improvement of motor function in paralyzed upper and lower limbs due to cerebrovascular disorders were considered to be most noticeable one to two months immediately after the onset. Remarkable improvement was believed to be difficult six months or more after the onset [1]. However, treatments for upper limb paralysis following a stroke that are pursuant to indications have recently become available, among which Constraint-Induced Movement Therapy (CIMT) [2] and Hybrid Assistive Neuromuscular Dynamic Stimulation (HANDS) therapy [3] are reportedly effective.

We started the combination therapy of Repetitive Transcranial Magnetic Stimulation (rTMS) and Novel Intervention Using rTMS and Occupational Therapy (NEURO®) in 2008 and have reported its mechanism and improvement effect in many papers [4-11]. A randomized trial demonstrated that low-frequency rTMS and physical therapy were effective for mild upper limb paralysis in the chronic phase [12]. Also, NEURO® was proven to be effective in a randomized trial of CIMT and NEURO® [9]. In addition, there were no serious adverse events from NEURO®, leading to the acknowledgement of NEURO® as a treatment method to safely and significantly improve motor function in upper limb paralysis in Japan and overseas [4-11].

In the present study, we aimed to further demonstrate the effect of NEURO® based on the results from multiple institutions, focusing on rehabilitation treatments in poststroke patients with upper limb paralysis during the recovery and chronic phases divided into three groups: the NEURO® group (combination of rTMS and intensive occupational therapy), the chronic phase group (combination of voluntary training and occupational therapy), and the recovery phase group (combination of voluntary training and occupational therapy).
Subjects and Methods

Subjects

The study period ran from April 2015 to March 2017. The subjects were consecutive patients with an FMA score of 46 points or more. The patients indicated for NEURO® were as defined in Table 1.

1. The Br-stage of the fingers of the paralyzed upper limb is stage IV to V (when assessing indication for treatment)
2. Aged 18 to 90 years old (when assessing indication for treatment)
3. The elapsed time from onset to treatment is one year or more.
4. History of only one stroke (stroke lesions are not bilateral)
5. Without noticeable cognitive impairment (26 points or more in the Mini-Mental State Examination)
6. Without active systemic disorders or psychiatric disorders that require aggressive medical treatment
7. Without a history of convulsive seizures for at least the last year
8. Without the existence of abnormal waves in electroencephalography such as epileptiform waves (Electroencephalogram inspection should be performed as screening only for patients with a history of convulsion or patients taking anticonvulsant medication)
9. Without the contraindication of items indicated in the guidelines proposed by Wasserman (presence of any metal in the head, presence of cardiac pacemaker, pregnancy and others)

Table 1: Criteria for the indication of NEURO®.

The subjects were divided into three groups comprised of the NEURO® group (combination of rTMS and intensive occupational therapy), the chronic phase group (combination of voluntary training and occupational therapy), and the recovery phase group (combination of voluntary training and occupational therapy). The patient background characteristics are shown in Table 2. There were five participating institutions: Izumi Memorial Hospital, Tokyo General Hospital, Jikei University Hospital, Nishi-Hiroshima Rehabilitation Hospital, and Kyoto Ohara Memorial Hospital (Table 2).

<table>
<thead>
<tr>
<th>Table 2: Clinical background of each group.</th>
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| **NEURO® group:** There were 34 patients indicated for NEURO® with an FMA score of 46 points or more at Izumi Memorial Hospital, Tokyo General Hospital, and Jikei University Hospital.

**Chronic phase group:** There were 27 patients with an FMA score of 46 points or more at Izumi Memorial Hospital and Kyoto Ohara Memorial Hospital.

**Recovery phase group:** There were 34 patients with an FMA score of 46 points or more who were hospitalized in Recovery Phase.
Rehabilitation Ward at Izumi Memorial Hospital and Nishi-Hiroshima Rehabilitation Hospital.

Methods

**NEURO® group:** Upon admission, the patients underwent an evaluation of motor function for the affected upper limbs, followed by a treatment session on the next day comprised of 40 min of low-frequency rTMS and 60 min of voluntary training. Two treatment sessions were conducted daily, in the morning and afternoon, for 20 sessions in total. Stimulation frequency with low-frequency rTMS was 1 Hz, which was performed with 2,400 stimuli daily. The stimulated area was the motor area of the healthy hemisphere responsible for finger movements, in other words, the area in which motor evoked potentials (MEP) of the first dorsal interosseous muscle in the unaffected upper limbs could be maximally induced on an electromyogram. The intensity of the stimulus was set to 90% of the motor threshold. A 70-mm figure-8 coil attached to MagPro R30 stimulator (MagVenture Company, Farum, Denmark) was used for application of rTMS.

**Chronic phase group:** Regular training was conducted within the range of health insurance treatment (within 13 units (20 min/unit) per week) without performing rTMS. In addition, voluntary training was supervised to adjust the total amount of the upper limb function training (13 units/week).

**Recovery phase group:** Regular training was conducted within 9 units (20 min/unit) daily with OT, PT, and ST, without performing rTMS. In addition, voluntary training was directed to adjust the total amount of the upper limb function training (3 units/day).

**Evaluation methods**

Clinical evaluation of the upper limb motor function was conducted using the FMA. As is widely known, the FMA [13] is a comprehensive evaluation method to test motor function, which judges the recovery of upper and lower limb motor function by focusing on the cooperative movement pattern and assesses balance, sensation, joint functioning, and others.

**Statistical analysis**

Changes in the FMA score before and after the treatment in each of the three groups were statistically analyzed using the Wilcoxon signed-rank test. A p value of less than 0.05 was considered statistically significant.

**Results**

In the present study, all of the patients completed the treatment. In addition, there were no adverse events associated with the treatment for any of the patients.

**FMA**

In the intragroup comparison of assessment items for the FMA, significant differences before and after the intervention were observed for statistics, item A, item B, and item C in the NEURO® group. In the intragroup comparison for assessment items of the FMA, significant differences before and after the intervention were observed for statistics, item A, item B, item C, and item D in the recovery phase group. There were no significant differences for any of the items in the chronic phase group (Table 3). And No significant differences in these item A, item B, item C, and item D between the three groups were noted at admission.

<table>
<thead>
<tr>
<th>Evaluation methods</th>
<th>NEURO® group (n=34)</th>
<th>Chronic phase group (n=27)</th>
<th>Recovery phase group (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At admission</td>
<td>At discharge</td>
<td>P value</td>
</tr>
<tr>
<td>Fugl-Meyer assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>53.7 ± 5.03</td>
<td>56.9 ± 4.34</td>
<td>0.0001</td>
</tr>
<tr>
<td>Score in A category</td>
<td>30.6 ± 2.41</td>
<td>32.3 ± 1.90</td>
<td>0.0162</td>
</tr>
<tr>
<td>Score in B category</td>
<td>7.44 ± 1.85</td>
<td>7.94 ± 1.80</td>
<td>0.0032</td>
</tr>
<tr>
<td>Score in C category</td>
<td>12.5 ± 2.06</td>
<td>13.1 ± 1.56</td>
<td>0.0088</td>
</tr>
<tr>
<td>Score in D category</td>
<td>3.12 ± 1.68</td>
<td>3.56 ± 1.56</td>
<td>0.0565</td>
</tr>
</tbody>
</table>

**Table 3:** Changes in the measures applied for the study.

For the intergroup comparison of changes of FMA items between the NEURO® group, chronic phase group, and recovery phase group, there were no significant differences between the NEURO® group and the recovery phase group, while the NEURO® group showed significant differences in total score, item A, and item B compared to the chronic phase group (Table 4).
In the chronic phase. In addition, because the average disease duration results of intragroup and intergroup comparison of FMA between the improvement to transfer to rehabilitation under the long-term care insurance system.

Table 4: Comparison between groups of the amount of change of each end-point of NEURO® group and the chronic phase group and the Recovery phase group.

Therefore, score improvement was observed in the NEURO® and recovery phase groups, while no improvement was observed in the chronic phase group.

Discussion

In the present study, subjects consisting of 95 consecutive patients with mild upper limb paralysis with an FMA score of 46 points or more were divided into 34 patients for the NEURO® group, 27 patients for the chronic phase group, and 34 patients for the recovery phase group to examine the effect of NEURO®. In general, patients with mild upper limb paralysis due to stroke are reported to reach a recovery plateau in approximately a few months. It was commonly believed that because the patients in the NEURO® and chronic phase groups were about 33.4 and 70.6 months after the disease onset, respectively, these patients would remain with mild upper limb paralysis with almost no improvement. Therefore, it is very significant that only the patients receiving NEURO® demonstrated an improvement in FMA scores even in the chronic phase. In addition, because the average disease duration for the recovery phase group was 3.35 ± 3.5 months, which is generally within the probable natural period of recovery, improvement in the FMA scores was highly conceivable. It is also important that improvement in the NEURO® group showed no significant difference compared to that in the recovery phase group. Based on the above results of intragroup and intergroup comparison of FMA between the NEURO®, recovery phase, and chronic phase groups, it was suggested that even after the period generally known as the period for the recovery of upper limb paralysis, NEURO® is expected to be effective in the improvement comparable to that in the recovery phase. Therefore, it is important that promising results were obtained demonstrating the improvement effect on patients indicated for NEURO®, even in the chronic phase group.

On the other hand, we often experience patients who once recovered upper limb function in the recovery phase decrease their upper limb function after transitioning to the chronic phase process. For rehabilitation under the current medical insurance system in Japan, due to the limited rehabilitation period covered by medical insurance, after 180 days from the onset date, it is common for patients to transfer to rehabilitation under the long-term care insurance system. In short, patients will transfer from one-on-one training to collective training. This means that in the rehabilitation with long-term care insurance, training will be conducted by groups using a machine and there are few trainings offered for individual diseases. Under these circumstances, trainings are not clearly divided between patients with muscle weakness due to disuse and patients with upper limb paralysis that take tremendous efforts to perform isolated movements. These findings suggest that, under the current situation, patients who hope to improve their function do not necessarily receive adequate rehabilitation. As functional improvement was recognized for chronic phase patients by conducting NEURO®, it is expected that adequate training combined with NEURO® will provide improved function to the selected subjects indicated for NEURO®. In addition, new approaches will be required in the future that will further improve function and QOL by aggressive use of the paralytic hand after the functional improvement of the upper limb.

Table 5: Limitations list of this study.

The limitations of the present study include the following (Table5). First, upper limb assessments other than FMA were not conducted. Because the FMA could not provide enough multilateral viewpoints, it was difficult to further grasp the factors of function improvement. Previous studies demonstrated that NEURO® would reduce spasticity through decreased excitability of the anterior horn cells in the spinal cord on the affected side. Therefore, in the future we will proceed with the study using the Modified Ashworth scale, which assesses muscle tone, Simple Test for Evaluating hand Function and Action Research Arm Test, which can evaluate more complex movements, and others. Second, although the amount of training in the recovery phase and chronic phase groups was adjusted to be equal to that in NEURO® group, voluntary training was included in the former two groups. Therefore, unification of the quality of training must be considered. The training in the NEURO® group was unified to two-hour individual rehabilitation/day and two-hour voluntary training/day, whereas the training in the recovery phase and the chronic phase groups included the intervention of only upper limb function training or a variety of contents, such as the training of daily chronic movements and higher brain function training. Because these trainings are involved in both medical insurance and long-term care insurance, it is challenging to strictly unify the them. Thus, to conduct NEURO®, it is necessary to reduce variations among institutions in the selection of target patients, the volume and content of trainings, and the evaluation method, which requires better and more sufficient communication among

participating institutions. We should make efforts to increase the number of subjects and to widely disseminate the therapy to the general public in the future. Also, we are planning to examine the effect of NEURO® from a wider viewpoint by implementing rTMS in the recovery phase group.

Conclusion

NEURO®, a treatment intervention that can be performed safely in patients with poststroke upper limb paralysis, was demonstrated to be effective in improving the motor function of paralyzed upper limbs. In addition, an effect comparable to that in the recovery period could be expected with the use of NEURO®, even in the chronic phase if the patients indicated for NEURO® were selected. As significant differences were observed in assessment methods, FMA, we would like to examine the significance of magnetic stimulation even in the recovery phase to further proceed with the improvement of upper limb function. Also, we will devote ourselves to the study to understand the therapy by phase, from the onset to the recovery and chronic phases, and to evaluate the universal quality of life.

Conflict of Interest

No conflict of interest was declared by the authors.

References