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Chapter XI

Combination Treatment of Repetitive Transcranial Magnetic Stimulation and Intensive Occupational Therapy: A Novel Therapeutic Approach for Upper Limb Hemiparesis after Stroke

Wataru Kakuda and Masahiro Abo
Department of Rehabilitation Medicine,
Jikei University School of Medicine, Tokyo, Japan

Abstract

Recently, low-frequency repetitive transcranial magnetic stimulation (rTMS) applied to the non-lesional hemisphere has been reported to improve motor function of the paretic upper limb after stroke. On the other hand, some clinical studies have confirmed the beneficial effect of intensive occupational therapy (OT) such as constraint-induced movement therapy for upper limb hemiparesis after stroke. Both low-frequency rTMS over the non-lesional hemisphere and intensive OT can facilitate neural activity of the lesional hemisphere, which compensates for impaired motor function of the paretic upper limb. We postulated that combined application of low-frequency rTMS and intensive OT might accelerate the improvement of motor function of the paretic upper limb in post-stroke patients. Therefore, we newly developed a 15-day in-patient protocol of combination treatment of these two interventions for this patient population. In the protocol, each patient was scheduled to receive 22 sessions of combination treatment with 20-min low-frequency rTMS of 1 Hz to the non-lesional motor cortex followed by intensive OT over 15 consecutive days. The program of intensive OT consisted of 60-min one-to-one training and 60-min self-exercise. The results of the multi-center study including more than 200 patients showed that our proposed protocol is a safe and feasible intervention. In addition, the protocol improved significantly motor function of the affected upper limb in studied patients. Furthermore, it seems that concomitant introduction of daily levodopa administration and botulinum toxin type A injection can augment the efficacy of the protocol. It may be a promising strategy to apply more potent modalities of TMS such as theta burst stimulation instead of conventional low-frequency rTMS, combined with intensive OT. In conclusion, our proposed combination treatment of low-frequency rTMS and intensive OT can be a novel therapeutic intervention for post-stroke patients with upper limb hemiparesis.

Introduction

In this chapter, we first discuss the therapeutic concept of repetitive transcranial magnetic stimulation (rTMS) combined with intensive occupational therapy (OT) for post-stroke patients with upper limb hemiparesis. In the second part, we describe our experience using the combination treatment of low-frequency rTMS and intensive OT in the same patient population. We also comment on future directions regarding this therapeutic modality in research and clinical practice.

Therapeutic Concept of rTMS Combined with Intensive OT for Upper Limb Hemiparesis after Stroke

Low-Frequency rTMS As a Therapeutic Tool

Transcranial magnetic stimulation (TMS) is a painless, safe procedure involving non-invasive brain stimulation (Hallett, 2007). Applying TMS in a repetitive manner, i.e., repetitive TMS (rTMS), can modulate local cortical neuronal excitability with effects ranging from up-regulation (facilitation) to down-regulation (suppression) of neuronal activity, depending on the frequency of stimulation (Huerta and Volpe, 2009). High-frequency rTMS (≥5 Hz) facilitates local neural activity, whereas low-frequency stimulation (≤ 1 Hz) depresses such activity (Chen et al., 1997; Maeda, Keenan, Tormos, Topka, and Pascual-Leone, 2000; Muellbacher, Ziemann, Boroojerdi, and Hallett, 2000; Wu, Sommer, Tergau, and Paulus, 2000). In cases of impaired neurological function due to stroke, rTMS as a therapeutic intervention should be applied to activate the cortical areas that compensate for the function. Using neuroimaging studies, some researchers revealed that the perilesional areas in the lesional hemisphere play an important role in motor functional recovery of the affected upper limb after stroke (Cramer et al., 1997; Feydy et al., 2002; Marshall et al., 2000; Weiller, Ramsay, Wise, Friston, and Frackowial, 1993). Based on these findings, we hypothesized that neural activation of the perilesional areas can induce motor functional recovery of the paretic upper limb after stroke. Considering the bidirectional effects of rTMS, two therapeutic approaches to activate the perilesional areas have been suggested; the direct and indirect approaches.

In the direct approach, facilitatory high-frequency rTMS is applied over the lesional hemisphere to directly up-regulate neural excitability in the perilesional areas (Figure 1). On the other hand, in the indirect approach, inhibitory low-frequency rTMS is applied to the non-lesional hemisphere to suppress neural activity of the non-lesional hemisphere with subsequent suppression of interhemispheric inhibition towards the lesional hemisphere. Finally, the perilesional areas are disinhibited from the interhemispheric inhibition, resulting in up-regulation of the neural activity in these areas (Figure 2).

Whether the direct or indirect approach is more beneficial for upper limb hemiparesis after stroke remains to be clarified. Rossi, Hallett, Rossini, and Pascual-Leone (2009) have suggested that high-frequency rTMS poses a clear risk of seizure induction In addition, low-frequency rTMS produces less site discomfort during stimulation than high-frequency rTMS.

Therefore, the indirect approach using low-frequency rTMS is safer and likely to be more widely applicable as a therapeutic intervention for upper limb hemiparesis after stroke compared with the direct approach using high-frequency rTMS.

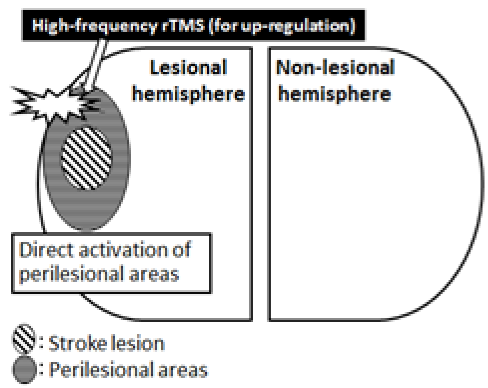


Figure 1. Direct approach. High-frequency rTMS is applied to the lesional hemisphere, to directly up-regulate neural excitability of the perilesional areas.

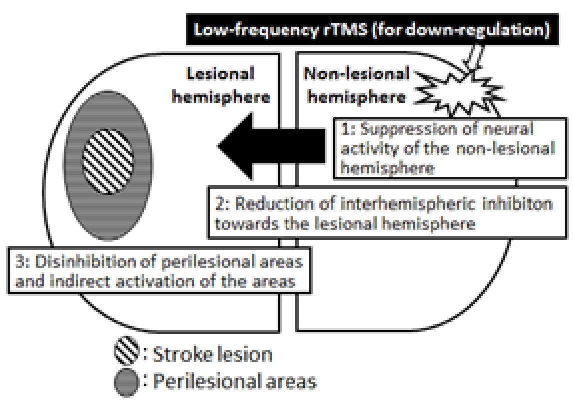


Figure 2. Indirect approach. Low-frequency rTMS is applied to the non-lesional hemisphere, resulting in the reduction of interhemispheric inhibition towards the lesional hemisphere. Subsequently, the perilesional areas are disinhibited from the interhemispheric inhibiton and activated.

Table 1. Reports of low-frequency rTMS over the non-lesional hemisphere for upper limb hemiparesis after stroke

Study	Intensity of stimulation (% of motor threshold)	Duration of one session (minutes)	No. of sessions (days)
Mansur et al. (2005)	100	10	1
Takeuchi et al. (2005)	90	25	1
Fregni et al. (2006)	100	25	5
Takeuchi et al. (2008)	90	25	1
Dafotakis et al. (2008)	100	10	1
Nowak et al. (2008)	100	10	1
Kirton et al. (2008)	100	20	8

* Pediatric stroke.

As shown in Table 1, the efficacy of low-frequency rTMS over the non-lesional hemisphere was established in many studies, and all showed significant improvement in motor function of the affected upper limb in post-stroke patients (Dafotakis et al., 2008; Fregni et al., 2006; Kirton et al., 2008; Mansur et al., 2005; Nowak et al., 2008; Takeuchi et al., 2005; Takeuchi et al., 2008).Notably, Fregni et al. (2006) indicated that improvement gained by daily application of low-frequency rTMS over a period of five consecutive days was maintained for up to 2 weeks after treatment cessation.

Based on these reports, we considered that low-frequency rTMS is a potentially useful therapeutic tool for upper limb hemiparesis after stroke.

Combined Application of Low-Frequency rTMS and Intensive OT

Based on the beneficial effect of low-frequency rTMS over the non-lesional hemisphere on motor function of the paretic upper limb after stroke, combining this rTMS modality with another therapeutic intervention with proven beneficial effects for upper limb hemiparesis could enhance the treatment outcome. As the results of a meta-analysis, Langhorne, Coupar, and Pollock (2009) indicated that constraint-induced movement therapy (CIMT), a typical form of intensive OT, is the most effective rehabilitative intervention available. In addition, the results of the Extremity Constraint Induced Therapy Evaluation (EXCITE) trial of more than 200 post-stroke patients confirmed the significant benefit of CIMT for treating upper limb hemiparesis after stroke (Wolf et al., 2006). As an underlying mechanism of beneficial effects with intensive OT, it has been reported that intensive OT can facilitate neural activity of perilesional areas in the lesional hemisphere (Lewy, Nichols, Schmalbrock, Keller, and Chakeres, 2001; Wittenberg et al., 2003). We thus speculated that the combination treatment of low-frequency rTMS and intensive OT could produce greater improvement in motor function of the affected upper limb, through further facilitation of neural activity in the lesional hemisphere, compared with rTMS alone. Figure 3 illustrates our therapeutic concept using such therapeutic interventions.

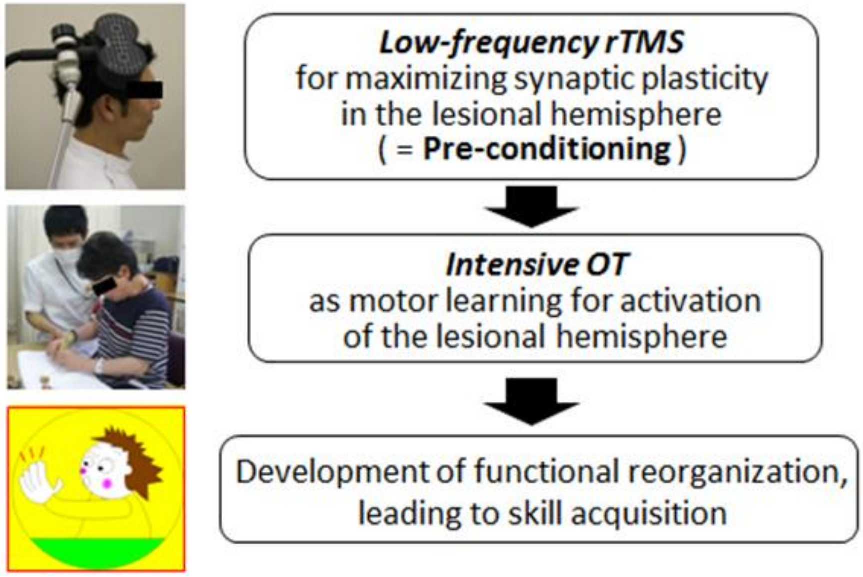


Figure 3. Therapeutic concept of our proposed combination treatment. Prior to intensive OT, low-frequency rTMS is applied as a pre-conditioning intervention for maximizing brain plasticity.

As a pre-conditioning intervention, low-frequency rTMS is applied first to maximize brain plasticity in the lesional hemisphere. Following rTMS application, intensive OT was then provided to further facilitate neural activity in the perilesional areas, with consequent beneficial functional reorganization in the lesional hemisphere. In other words, we assumed that low-frequency rTMS over the non-lesional hemisphere conditions the compensating areas in the lesional hemisphere to be more responsive to the effects of intensive OT.

In-Patient Protocol of Combination Treatment

In 2008, we introduced the combination treatment of low-frequency rTMS and intensive OT as a 15-day protocol for post-stroke in-patients with upper limb hemiparesis at our university hospital (Kakuda et al., 2010). After confirming the protocol safety in a small number of patients at our university hospital, some other hospitals in Japan also started to provide the same protocol of combination treatment. Currently, eight hospitals in different parts of Japan (Jikei University Hospital, Jikei Daisan Hospital, Shimizu Hospital, Tokyo General Hospital, Nishi-Hiroshima Rehabilitation Hospital, Aizawa Hospital, Suwanomori Hospital, and Kimura Hospital) use our proposed protocol of the combination treatment as an in-patient intervention. All these hospitals have an at least 30-bed ward/section specially equipped for long-term rehabilitation of stroke patients, two or more board-certificated physicians, and at least five occupational therapists with expertise in stroke rehabilitation. Prior to the introduction of the protocol, physicians and therapists at each institution received training at our university hospital. All participating hospitals use the same inclusion criteria, therapeutic protocol, and clinical measures for assessment of the protocol efficacy.

Inclusion Criteria

The following are the currently used criteria in the above hospitals to determine the suitability of post-stroke patients for the treatment: *1)* Brunnstrom stage for hand-fingers of 3-5 (ability, at least subjectively, to flex all the fingers of the affected upper limb in full range of motion); *2)* age at intervention of 18-90 years; *3)* more than 12 months between the onset of stroke and treatment; *4)* history of a single stroke only (no bilateral cerebrovascular lesion); *5)* no cognitive impairment with a pretreatment Mini Mental State Examination score of more than 26; *6)* clinical confirmation of the plateau state, representing no increase in the Fugl-Meyer Assessment (FMA) score assessed by an occupational therapist from the institution in the latest 3 months; *7)* no active physical or mental illness requiring medical management; *8)* no recent history of seizure (within one year preceding the intervention); *9)* no documented epileptic discharge on pretreatment electroencephalogram; *10)* no current use of antiepileptic medications for the prevention of seizure; and, *11)* no pathological conditions known to be contraindications for rTMS, as listed in the guidelines of Wassermann (e.g., intracranial implants, cardiac pacemakers, pregnancy) (Wassermann, 1998).

Time Schedule of 15-Day Protocol

All patients were hospitalized in order to receive the 15-day protocol. During hospitalization, each subject received 22 treatment sessions, each comprising 20 minutes for application of low-frequency rTMS and 120 minutes of intensive OT (two sessions per day, except for the days of admission/discharge and Sundays) (Figure 4).

Application of Low-Frequency rTMS

At all hospitals, the rTMS was delivered using a 70-mm figure-8 coil and MagPro R30 stimulator (MagVenture Company, Farum, Denmark). In each 20-minute session, low-frequency rTMS of 1,200 pulses of 1 Hz was applied over the motor cortex of the non-lesional hemisphere, at the site that elicited the largest motor-evoked potentials (MEPs) in the first dorsal interosseous (FDI) muscle of the unaffected upper limb (confirmed by surface electromyographic recording).

The intensity of the stimulation was set at 90% of motor threshold of the FDI muscle, which was defined as the lowest intensity of stimulation that could activate MEPs in the muscle.

For safety monitoring, a physician at each hospital briefly examined the patient before and after each rTMS session, paying attention to the possible development of adverse effects of rTMS (e.g., headache, nausea, convulsion), appearance of new neurological symptoms (e.g., motor disturbance of the unaffected limbs), or deterioration of upper limb hemiparesis.

	Thursday	Friday-Saturday	Sunday	Monday-Saturday	Sunday	Monday-Wednesday	Thursday
Morning	Admission	Low-frequency rTMS (20min)	No treatment	Low-frequency rTMS (20min)	No treatment	Low-frequency rTMS (20min)	Post-therapy evaluation
		One-to-one training (60min)		One-to-one training (60min)		One-to-one training (60min)	
		Self-exercise (60min)		Self-exercise (60min)		Self-exercise (60min)	
Afternoon	Pre-therapy evaluation	Low-frequency rTMS (20min)		Low-frequency rTMS (20min)		Low-frequency rTMS (20min)	Discharge
		One-to-one training (60min)		One-to-one training (60min)		One-to-one training (60min)	
		Self-exercise (60min)		Self-exercise (60min)		Self-exercise (60min)	

Figure 4. Time schedule of 15-day protocol of combination treatment. Except for days of admission/discharge and Sundays, patients were scheduled to receive two sessions of rTMS and intensive OT daily.

Rehabilitative Program of Intensive OT

The program of intensive OT comprised two components: a 60-minute one-to-one training and a 60-minute self-exercise. The one-to-one training, which was provided by an occupational therapist, mainly involved shaping practices (e.g., reaching forward to move a cup from one place to another, writing letters and pictures using a pencil, wiping the surface of the table with a towel, picking up a hairbrush and combing hair) and repetitive task practices (e.g., clay squeezing and molding, pinching small coins, gripping a small ball). In both components of the protocol, patients were instructed to concentrate on use of the affected upper limb.

Although both of these two practices were always included at almost the same proportion of training time (usually 30 minutes for shaping practice and 30 minutes for repetitive task practice) in the one-to-one training program of each patient, the program was tailored by the therapist to suit the individual patient, based on motor function of the affected upper limb and lifestyle of the patients (e.g., occupation, interest, household work). Certain conventional approaches such as facilitation techniques and manual dexterity exercises were also sometimes included in the program. During the hospitalization, the program was modified following motor functional improvement of the affected upper limb.

All the one-to-one training tasks were generally supervised in a face-to-face fashion by an occupational therapist. Positive verbal guidance, encouragement, and feedback were frequently provided so as to achieve the best performance for the selected tasks. The therapists also provided “hands-on” facilitation of movement and inhibition of inappropriate muscle contraction, if necessary.

Following the one-to-one training session, self-exercise was administered in another quiet room without any supervision by the therapist (the room was under continuous video monitoring using built-in-camera for patient safety). Prior to each self-exercise, each patient received specific written instructions for tasks similar to those applied in the one-to-one training, generally involving 3-8 tasks per self-exercise session, with some rest breaks of a few minutes.

After each self-exercise session, the occupational therapists checked and reviewed performance of the tasks through an interview. Problem associated with the tasks were approached aggressively in the following one-to-one training session.

Clinical Evaluation of Upper Limb Motor Function

To determine the effect of the therapeutic protocol on motor function of the affected upper limb, FMA and Wolf Motor Function Test (WMFT) were applied on the days of admission and discharge, and four weeks after discharge whenever possible. The FMA includes 33 items for the evaluation of upper limb motor function (Gladstone, Danells, and Black, 2002; Platz et al., 2005). As each item is rated on a three-point ordinal scale (0=cannot perform, 1=can perform partially, 2=can perform fully), 66 points is the maximum possible score for motor performance of the upper limb. The WMFT includes 15 timed tasks for the evaluation of upper limb motor function, with the performance time of each timed task recorded (Morris, Uswatte, Crago, Cook, and Taub, 2001; Wolf et al., 2001). When the task is not completed within 120 seconds, the performance time of the task was recorded as 120 seconds. For statistical analysis, the mean value of WMFT performance time of 15 tasks was transformed to a natural logarithm as WMFT log performance time, to normalize the skewed distribution of the data, as applied in the analysis of data of the EXCITE trial (Wolf et al., 2006).

Clinical Results

By the end of January 2011, 204 post-stroke patients had received the protocol at some of the above mentioned hospitals. In this section, we describe the clinical results of the protocol in these patients (Kakuda et al., 2012).

Clinical Features of Studied Patients

As shown in Table 2, the mean age of the patients at admission was 58.5 ± 13.4 years. The mean time between stroke onset and the intervention was 5.0 ± 4.5 years. Stroke was classified into intracerebral hemorrhage in 107 patients and cerebral infarction in 97 patients.

Safety and Feasibility of the Protocol

The 15-day treatment protocol was completed by all patients. No significant change in the vital signs was observed in any patients throughout the in-patient treatment. Furthermore, none of the patients developed new symptoms or noticed any deterioration of motor function in the upper limb during hospitalization. In 79 patients who received follow-up evaluation at four weeks after discharge, no new adverse symptoms or signs were recorded after the discharge.

Based on these observations, we concluded that the protocol was safe and feasible.

Treatment Outcome on Motor Function of the Affected Upper Limb

The significance of the median changes in FMA score and WMFT log performance time following the treatment was analyzed using the signed Wilcoxon's rank sum test for paired samples. All statistical analyses were performed using The Statistical Package for Social Sciences, v17.0 (SPSS Inc., Chicago, IL).

Based on the data from all 204 participating patients, the median FMA score increased significantly from 47 (36-54) [median (interquartile range)] points at admission to 51 (42-57) points at discharge (Figure 5). Similarly, the 15-day protocol significantly reduced the median WMFT log performance time from 3.23 (1.70-4.07) to 2.51 (1.36-3.86) (Figure 6).

Table 2. Demographic data of the studied patients

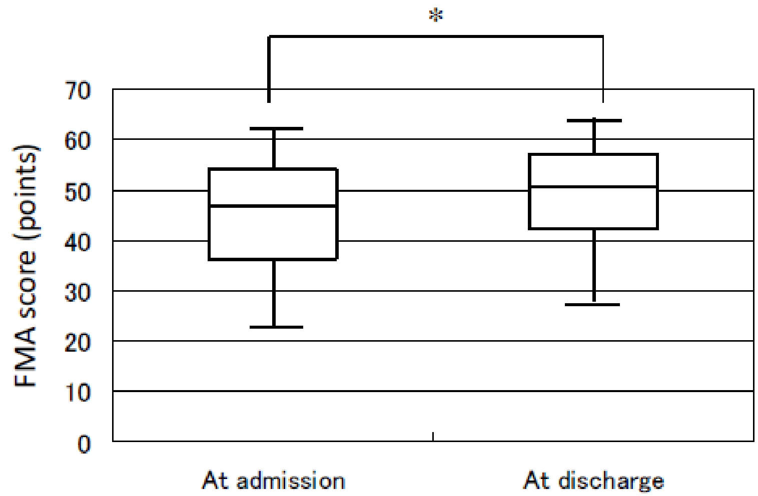
Age at admission, years	58.5 ± 13.4
Gender	
Females	73 (36)
Males	131 (64)
Time since stroke onset, years	5.0 ± 4.5
Subtype of stroke	
Intracerebral hemorrhage	107 (53)
Cerebral cortical infarction	27 (13)
Lacunar infarction	70 (34)
Side of upper limb hemiparesis	
Dominant hand	124 (61)
Non-dominant hand	80 (39)

Values are numbers (%) or mean ± standard deviation.

In 79 patients who were also evaluated at 4 weeks after discharge, both the increased FMA score and decreased WMFT log performance time remained significant compared to the respective values at admission [FMA: 48 (range, 34-53) points at admission, 51 (38-57) points at discharge, 50 (34-56) points at 4 weeks after discharge; WMFT log performance time: 2.81 (1.42-4.08) at admission, 2.20 (1.25-3.78) at discharge, 2.01 (1.31-3.94) at 4 weeks after discharge]. These results suggested that our proposed 15-day protocol improves motor function of the paretic upper limb and that the improvement is maintained for at least 4 weeks after cessation of the protocol.

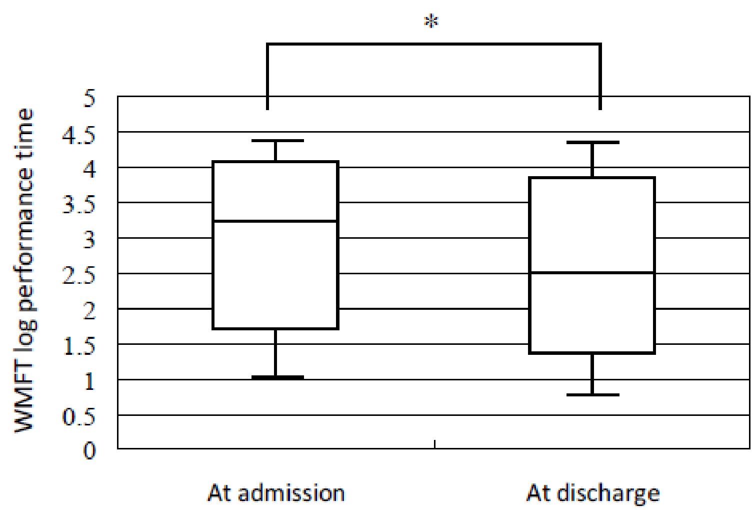
Baseline Features Affecting Treatment Outcome

In order to identify the factors that correlated significantly with the outcome (i.e., significant change in FMA score and WMFT log performance time), linear regression analysis was performed using the following five baseline characteristics: age, gender, time since stroke onset, subtype of stroke (intracerebral hemorrhage/cerebral cortical infarction/lacunar infarction), and side of upper limb hemiparesis (dominant hand/non-dominant hand).



*p<0.001.

Figure 5. Changes in FMA score in all studied patients. Bars represent the median, and 5th, 25th, 75th, and 95th percentiles.



*p<0.001.

Figure 6. Changes in WMFT log performance time in all studied patients. Bars represent the median, and 5th, 25th, 75th, and 95th percentiles.

When FMA score or WMFT log performance time was selected as the dependent variable, no significant relationship with any of the five parameters was found, indicating that no clinical factor tested thus far definitely influences the functional response to the protocol.

Future Directions in Research and Clinical Practice

The present study suggested that the combination treatment of low-frequency rTMS and intensive OT safely improves motor function of the paretic upper limb in post-stroke patients.

However, the described protocol was not necessarily satisfactory for all the patients treated, and further improvements in efficacy and extent of benefit of the protocol are needed to ensure that more patients receive the therapeutic effects.

We have therefore proposed further modifications to the protocol for future clinical use in improving motor functional recovery, and initiated pilot studies to assess the safety and effect of these modified protocols. The ideas involve levodopa administration, botulinum toxin injection, and the application of more potent TMS modalities.

Concomitant Administration of Levodopa

Some neurotransmitters modulate brain plasticity after brain damage. In particular, noradrenaline in the brain seems important for facilitating motor functional recovery in the brain following damage (Boyeson and Feeney, 1989). However, such a molecule can have severe adverse effects on various systems such as the cardiovascular system.

On the other hand, administration of levodopa, which is partly metabolized to noradrenaline in the brain, is considered safe and feasible to increase the brain concentration of noradrenaline (Nutt and Fellman, 1984).

A recent randomized, prospective, double-blinded study of post-stroke patients found that levodopa administration of 100 mg daily for three weeks in addition to physiotherapy could enhance motor recovery in post-stroke hemiparetic patients (Scheidtmann, Fries, Muller, and Koenig, 2001).

Furthermore, none of these patients showed severe adverse effects associated with levodopa, indicating its safety and feasibility in such a patient population. Therefore, we hypothesized that concomitant administration of levodopa could further facilitate the beneficial plastic changes in the brain produced by our combination treatment.

In other words, levodopa administration could conditions the brain to be more responsive to the combination treatment of rTMS and intensive OT. Figure 7 illustrates our novel protocol featuring levodopa administration (Kakuda et al., 2011b). Patients were scheduled to receive a daily oral administration of 100 mg levodopa for one week prior to admission. If the administration was tolerated for one week, the full 15-day in-patient protocol was commenced, along with levodopa administration. The administration was continued until four weeks after the discharge.

We recommend an aggressive administration of levodopa concomitantly with our combination treatment, as such a regimen is easy to clinically administer and is not associated with a high risk of adverse effects.

Pre-Treatment Injection of Botulinum Toxin Type A

For some patients with marked upper limb spasticity as well as upper limb hemiparesis, it seemed that our current protocol of combination treatment did not work well (Kakuda et al., 2011c).

Outpatient treatment		In-patient combination treatment					Outpatient treatment
One week before admission			On the day of admission	2-14 days of admission (except for Sundays)	On the day of discharge		Four weeks after discharge
Start of levodopa administration (orally 100mg/day)	➡	➡	**(Continue to administrate)**		➡	➡	
		AM	Admission	Low-frequency rTMS (20 min) One-on-one training (60 min) Self-training (60 min)	Post-therapy evaluation and instruction for self-training		Follow-up evaluation
		PM	Pre-therapy evaluation	Low-frequency rTMS (20 min) One-on-one training (60 min) Self-training (60 min)	Discharge		

Figure 7. Novel protocol featuring levodopa administration. Patients are requested to receive daily levodopa administration concomitantly with the combination treatment of rTMS and intensive OT.

For such patients, a focal injection of botulinum toxin type A (BTXA) prior to the combination treatment is recommended. In recent years, BTXA has been used to control focal spastic hypertonia in patients with upper motor neuron disturbances. Focal injection of BTXA inhibits the release of acetylcholine at the neuromuscular junction and reduces spasticity of the injected muscle (Brashear et al., 2002; Richardson et al., 2000). Since the BTXA is most effective 4-8 weeks after the injection, the focal injection should be performed at the clinic 4 weeks prior to the in-patient combination treatment (Kaji et al., 2010).

The selected dose was based on the severity of spasticity and the volume of the target muscles. Based on previous reports, the selected target muscles were in the following order: biceps brachii muscle, flexor carpi radialis muscle, flexor carpi ulnaris muscle, flexor digitorum superficialis muscle, flexor digitorum profundus muscles, flexor pollicis longus muscle, and adductor pollicis muscle (Brin, 1997). The maximum total dose of injected BTXA was 240 units. The pilot study revealed significant improvement in motor function of the affected upper limb, in addition to a significant reduction in spasticity following the intervention. It is possible that the beneficial effects of our proposed protocol will be reduced with the disappearance of the toxin effect; however, the anti-spastic effect of intramuscular BTXA could be successfully maintained by repeated injections 12-20 weeks apart (Bakheit et al., 2004; Elovic et al., 2008). It is expected that such a procedure can maintain the improved motor function in patients who received our combined therapeutic protocol over a long period of time (beyond the expiration of the first injection of BTXA) when BTXA is injected at regular intervals.

Application of More Potent TMS Modalities for Neuromodulation

Recently, certain TMS modalities have been reported to be more powerful than conventional rTMS in modulating brain plasticity, including theta burst stimulation (TBS), rTMS with priming stimulation (primed rTMS), paired-pulse stimulation, and quadro-pulse stimulation (Cardenas-Morales, Nowak, Kammer, Wolf, and Schonfeldt-Lecuona, 2010; Carey, Anderson, Gillick, Whitford, and Pascual-Leone, 2010; Hamada et al., 2007; Huang, Edwards, Rounis, Bhatia, and Rothwell, 2005; Iyer, Schleper, and Wassermann, 2003; Thickbroom, Byrnes, Edwards, and Mastaglia, 2006). Among these modalities, we suggest the application of TBS and primed rTMS instead of the conventional rTMS used in our current protocol, since the safety of both these other modalities have been confirmed and some reports describing their clinical use are already published. The TBS comprises three pulses of 50 Hz delivered every 200 ms, simulating a theta-like rhythm. The pattern of delivery of TBS (continuous TMS versus intermittent TBS) is crucial in determining whether the excitability of the motor cortex is increased (intermittent TBS) or decreased (continuous TBS), with both deliveries inducing after-effects that last longer than any other known rTMS protocol (Cardenas-Morales et al., 2010; Huang et al., 2005). Other advantages of TBS include the shorter application time and the lower stimulation intensity needed to modulate cortical excitability, compared to conventional rTMS modalities. Therefore, a promising strategy for the application could be continuous TBS over the non-lesional hemisphere instead of the conventional low-frequency rTMS, combined with intensive OT for upper limb hemiparesis after stroke. Confirming the usefulness of primed rTMS, Iyer, Schleper, and Wassermann (2003) demonstrated that immediately preceding 1-Hz rTMS with "priming" trains of 6-Hz rTMS caused significantly greater depression of cortical excitability in the stimulated hemisphere than without such priming. This TMS modality also can be clinically applied as an intervention for suppressing neural activity of the non-lesional hemisphere. In our novel protocol featuring this 6-Hz primed low-frequency rTMS, a session of priming stimulation comprising 10 minutes of intermittent 5-Hz rTMS given in 5-s trains with 25-s intervals between trains (Kakuda et al., 2011a). Immediately following the priming stimulation, low-frequency pulses of 1 Hz were applied for 20 min. The result of a pilot study of combined 6-Hz primed low-frequency rTMS and intensive OT showed the beneficial effect of this protocol for upper limb hemiparesis after stroke.

Conclusion

Low-frequency rTMS applied together with intensive OT significantly improved motor function of the paretic upper limb after stroke, and such improvement was not associated with any adverse events. Although its efficacy needs to be confirmed in a randomized controlled trial with a control group, we are confident that the protocol is therapeutically beneficial for post-stroke patients with upper limb hemiparesis. We expect that the efficacy of the protocol could be improved with the introduction of concomitant use of pharmacological approaches and application of more potent TMS modalities.

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