

Therapeutic administration of atomoxetine combined with rTMS and occupational therapy for upper limb hemiparesis after stroke: a case series study of three patients

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Abstract Atomoxetine, a selective noradrenaline reuptake inhibitor, has been reported to enhance brain plasticity, but has not yet been used in stroke patients. We reported the feasibility and clinical benefits on motor functional recovery of the combination of repetitive transcranial magnetic stimulation (rTMS) and intensive occupational therapy (OT) in stroke patients. This pilot study was designed to evaluate the additive effects of oral atomoxetine to rTMS/OT in post-stroke hemiparetic patients. The study included three post-stroke patients with upper limb hemiparesis. Treatment with 40 mg/day atomoxetine commenced 2 weeks before admission. After confirming tolerance, the dose was increased to 120 mg/day. Low-frequency rTMS/OT was provided daily for 15 days during continued atomoxetine therapy. Motor function of the affected upper limb was evaluated with the Fugl-Meyer Assessment and Wolf Motor Function test. All patients completed the protocol and showed motor improvement up to 4 weeks after the treatment. No atomoxetine-related side effects were noted. Our protocol of triple therapy of atomoxetine, low-frequency rTMS, and OT is safe and feasible intervention for upper limb hemiparesis after stroke.

Keywords Stroke · Upper limb hemiparesis · Atomoxetine · Repetitive transcranial magnetic stimulation · Neurorehabilitation

Introduction

Stroke is one of the leading causes of adult long-term disability [1]. The consequent neurological deficits demand rehabilitative training for functional recovery. In this clinical setting, brain plasticity is a major issue in the clinical management [2, 3]. Brain plasticity in stroke patients can be interpreted to reflect the capacity of the brain to reorganize after the cerebrovascular lesion in order to compensate for neurological deficits. Any improvement in brain plasticity is expected to facilitate post-stroke functional recovery. It has been reported that modulation of the noradrenergic system can influence brain plasticity in human [4]. Several studies have reported that administration of amphetamine and methylphenidate improved functional outcome of stroke patients [5–9]. However, adverse cardiovascular events such as stroke, myocardial infarction, and sudden death and abuse potential associated with these drugs limit their use clinically in stroke rehabilitation [10, 11].

On the other hand, atomoxetine, a selective noradrenaline reuptake inhibitor, increases intracerebral concentration of noradrenaline similar to amphetamine and methylphenidate [12, 13]. Importantly, atomoxetine has no serious cardiovascular adverse effects and no abuse potential unlike other noradrenergic drugs [14, 15]. In addition, recently published papers have indicated that atomoxetine can influence brain plasticity and motor learning in human [16–19]. To our knowledge, there is no information at present on the therapeutic effects of atomoxetine in post-stroke patients.

We have reported the use of repetitive transcranial magnetic stimulation (rTMS) combined with intensive occupational therapy (OT) for treatment of post-stroke patients with upper limb hemiparesis [20–22]. The

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combination treatment proved to be safe and beneficial for such patient population. It is considered that this favorable response is mainly due to the development of functional reorganization in the lesional hemisphere.

Based on these reports and our experience, we hypothesized that the beneficial effects of the combination of rTMS and OT in post-stroke hemiparetic patients would be facilitated by simultaneous treatment with atomoxetine, through further enhancement of brain plasticity. The aim of this pilot study was to provide an initial evaluation of the safety, feasibility, and efficacy of the triple-element protocol featuring atomoxetine administration, rTMS, and OT for post-stroke patients with upper limb hemiparesis.

Subjects and methods

The study protocol and intervention were approved by the ethics committee of our university. Three post-stroke patients with upper limb hemiparesis were recruited for this case series study. All of them were referred to our department as potential candidates for this study. Informed consent was obtained from the three patients. The inclusion criteria were almost similar to those applied in our previous studies on rTMS and OT, namely [20–22]: (1) Brunnstrom stage for hand-fingers of 3–5 (ability, at least, subjectively to flex all fingers of the affected upper limb in full range of motion). (2) Age at intervention of 18–80 years. (3) Time between stroke onset and intervention of more than 12 months. (4) History of a single stroke only (no bilateral cerebrovascular lesion). (5) No apparent cognitive impairment with Mini Mental State Examination score of less than 26. (6) No active physical or mental illness requiring medical management. (7) No history of seizure within 1 year preceding the intervention. (8) No documented epileptic discharge on the electroencephalogram. (9) No pathological conditions known to be contraindications for rTMS in the guidelines suggested by Wassermann [23]. In addition, patients in whom atomoxetine use was considered to be contraindicated were excluded from the study. The contraindications to the drug included presence of liver dysfunction, renal dysfunction, and heart diseases, such as myocardial infarction, symptomatic arrhythmia, severe, or uncontrollable hypertension.

The clinical characteristics of the three patients are shown in Table 1. Two patients suffered intracerebral hemorrhage and one patient suffered from cerebral infarction more than 1 year ago. The general condition of three patients after stroke onset was satisfactory without any other neurological disorders. They experienced some difficulty in ADL, although upper limb hemiparesis was not severe at study entry.

Figure 1 outlines our 4-week protocol featuring atomoxetine, rTMS and OT. Oral administration of atomoxetine commenced 2 weeks before admission. After confirming that no adverse events occurred with atomoxetine use, low-frequency rTMS and rehabilitative training was initiated as an inpatient intervention. During 15-day hospitalization, each patient was scheduled to receive 22 treatment sessions of rTMS and OT (two sessions per day, except for Sundays). The administration of atomoxetine was continued until discharge from the hospital. Motor function of the affected upper limb was evaluated serially 2 weeks before admission (on the commencement of atomoxetine therapy), at the time of admission and discharge, and 4 weeks after their discharge. In order to assess the safety of the protocol, patients were monitored clinically by daily clinical and neurological examinations during the treatment period. All patients were informed about the nature of this study and possible adverse effects of atomoxetine.

Treatment with atomoxetine

Atomoxetine was administered orally every day from two weeks before admission until discharge (Fig. 1) at an initial dose of 40 mg/day during the first week, and then increased to 80 mg/day (subject to tolerance of the initial dose). Furthermore, the dose was increased to 120 mg/day during the 15-day hospitalization if no adverse events appeared. The prescribed dose was taken before breakfast. Patients were monitored daily by the attending physician for the possible development of known adverse effects of atomoxetine such as nausea, headache, increased blood pressure, and tachycardia.

Application of rTMS

Low-frequency rTMS was applied using a 70-mm figure-of-8 coil and MagPro R30 stimulator (MagVenture Company, Farum, Denmark). According to the current safety recommendations, focal rTMS of 1 Hz was applied over the non-lesional primary motor cortex. Each rTMS session consisted of 1200 pulses, lasting 20 min. The optimal site of stimulation on the skull was defined as the location where the largest motor evoked potentials (MEPs) in the first dorsal interosseous (FDI) muscle of the unaffected upper limb was elicited on surface electromyography. The resting motor threshold (MT) of the FDI muscle of the unaffected upper limb was defined as the minimum stimulus intensity that produced a minimal motor evoked response of the muscle at rest. According to the measured resting MT, the intensity of stimulation was set at 90 % of the MT for the FDI muscle. A physician from our department briefly examined the patient before and after each

Table 1 Clinical characteristics of the studied patients

	Patient 1	Patient 2	Patient 3
Age at admission (years)	55	63	47
Sex	Male	Female	Female
Height (cm)	160	150	152
Weight (kg)	62	50	57
Time from onset of stroke (months)	19	15	37
Type of stroke	ICH	ICH	ICH
Site of lesion on T2-weighted MRI	Right putamen	Left thalamus	Left putamen
Side of upper limb hemiparesis	Left	Right	Right
Handedness	Right	Right	Right
BRS for hand-fingers/upper limb	5/5	5/4	5/5
Medical history	Hypertension valsartan,	Hypertension telmisartan,	Hypertension aspirin,
Medications	Nifedipine, doxazosin	Trichlormethiazide, doxazosin	Amlodipine, doxazosin

ICH intracerebral hemorrhage, CI cerebral infarction, BRS Brunnstrom recovery

	Outpatient treatment			Inpatient treatment		
	Two weeks before admission	One week before admission		On day of admission	2-14 days of admission (except for Sunday)	On day of discharge
Atomoxetine	40 mg/day for 7 days	80 mg/day for 7 days		120 mg/day for 15 days		
				AM	Admission	Post-treatment evaluation
					Low-frequency rTMS (20 min) One-on-one training (60 min) Self-exercise (60 min)	
				PM	Pre-treatment evaluation	Discharge
					Low-frequency rTMS (20 min) One-on-one training (60 min) Self-exercise (60 min)	

Fig. 1 Treatment protocol: treatment with atomoxetine commenced 2 weeks before admission. During the 15-day hospitalization, two sessions of low-frequency rTMS and rehabilitative training were provided daily, with concomitant use of atomoxetine

rTMS session, to confirm their general condition and assess the development of possible adverse event with rTMS.

Intensive occupational therapy

One session of intensive OT consisted of one-to-one training for 60 min followed by self-exercise for 60 min. An occupational therapist at our department introduced the one-to-one training in a face-to-face fashion. This training mainly involved the application of shaping (e.g., reaching forward to move a cup from one place to another, writing letters and pictures using a pencil) and repetitive task practice techniques (e.g., clay squeezing and molding, pinching small coins). This program was tailored by the occupational therapist to suit the individual patient based on the motor function deficit in the affected upper limb and patient's lifestyle. Conventional approaches, such as

facilitation techniques and manual dexterity exercise, were occasionally provided. The 60-minute self-exercise was conducted in another quiet room without any supervisor. The tasks for the self-exercise were similar to those applied in the one-to-one session. At discharge, patients were provided with oral and written instructions prepared by the occupational therapist for daily home exercise.

Outcome measures for motor function

The Fugl-Meyer Assessment (FMA) and Wolf Motor Function Test (WFMT) were applied as the main measures of motor function of the affected upper limb. FMA is a performance-based quantitative measure for the assessment of various impairments in post-stroke patients, with assessment of upper limb motor function comprising 33 items of measurement [24]. The maximum possible motor

performance score for upper limbs is 66 points, with each item rated to a 3-point (0-1-2) ordinal scale. The 15 timed tasks of WMFT were applied and total performance time was calculated [25]. Furthermore, upper limb spasticity was evaluated on the affected side using a 6-graded modified Ashworth Scale (MAS) [26].

Results

Table 1 shows the clinical characteristics of the three patients. All of three patients completed the 15-day inpatient protocol without showing any side effects to atomoxetine. No neurological deterioration was noted. Furthermore, no adverse symptom has developed during 4 weeks after their discharge in any patient.

As shown in Table 2, one patient showed improvement in FMA score only after treatment with atomoxetine at the time of admission. The 15-day triple-element protocol increased the FMA score and shortened the sum of performance times for 15 tasks in WMFT. In addition, the motor improvement was maintained for up to 4 weeks after discharge in all the patients. Following the same

treatment, two patients showed a decrease in the MAS score of the wrist flexor muscles and in that of the finger flexor muscles. Patient 1 and 2 became able to pinch with thumb and one finger after the intervention, and patient 1 acquired the ability to turn over pages of a newspaper and felt more comfortable washing his face and wearing a belt using the affected upper limb. Patient 2 became able to drink from a cup, eat food with a fork, brush teeth, wash the face, and shampoo the hair with the affected limb. She also reported significant improvement in the smoothness and speed of movement of the affected upper limb. After the intervention, patient 3 were easily capable of reaching a cup and typing at a keyboard with the affected upper limb.

Discussion

All of three patients safely completed the 15-day inpatient triple-element protocol. In three patients, the protocol increased FMA score and decreased WMFT total performance time, suggesting motor function improvement in the affected upper limb.

Table 2 Evaluation of motor function in the paretic upper limb

	Patient 1	Patient 2	Patient 3
FMA (points)			
2 weeks before admission	50	48	59
At admission	50	52	59
At discharge	56	56	63
4 weeks after discharge	58	52	63
Total performance time of 15-task WMFT (s)			
At admission	83	135	41
At discharge	56	92	35
4 weeks after discharge	71	79	35
MAS (finger flexors/wrist flexors)			
At admission	1/1	1/1+	1/1
At discharge	1/1	1/1	0/1
4 weeks after discharge	1/1	1+/1	1/1
ADL performance using paretic upper limb			
At admission	Not using paretic hand in ADL, apart from washing face	Not using paretic hand	Using paretic hand in almost all ADL
At discharge	Able to turn over pages of a newspaper	Able to drink using cup, eat food with fork, brush teeth, wash own face and hair	Able to smoothly reach a cup and type at a keyboard
4 weeks after discharge	Same as at discharge	Same as at discharge	Same as at discharge

FMA Fugl-Meyer assessment, WMFT wolf motor function test, MAS modified Ashworth scale

The noradrenergic system plays an important role in functional recovery after stroke, and activation of this system is known to promote the plastic changes in the brain [4–6]. Several clinical studies have tested the effects of amphetamine and its related drug methylphenidate, which enhances adrenergic neurotransmission secondary to the release of noradrenaline, in stroke rehabilitation and reported the beneficial effects on functional recovery after stroke [7–9]. However, one factor that limits the use of these drugs is the range of potentially serious effects, such as hypertension, which could lead to cardiovascular accidents, arrhythmia, behavioral arousal, and hypermotility [10, 11]. These effects raise concern on the adverse actions of the drugs in stroke patients. Therefore, the clinical use of these drugs in stroke rehabilitation has not been widespread.

On the other hand, atomoxetine affects the regulation of noradrenaline as a highly selective inhibitor of the presynaptic noradrenaline transporter [12]. Atomoxetine is reported to increase intracerebral concentrations of norepinephrine [13]. Furthermore, atomoxetine lacks affinity for dopaminergic and serotonergic receptors, has no abuse potential, and has minimal cardiovascular side effects [14, 15]. These features provide important advantages for atomoxetine in its use for humans. Atomoxetine was recently approved by The U.S. Food and Drug Administration and The Japan Health, Labour and Welfare Ministry for the treatment of attention deficit hyperactivity disorder. Furthermore, atomoxetine was reported to improve plastic changes in the human brain. For example, Foster et al. evaluated the effect of atomoxetine on motor learning in ten healthy subjects in a double-blind randomized study, and reported significant enhancement of brain plasticity after atomoxetine therapy [16]. Similarly, Gilbert et al. demonstrated a significant increase in facilitation and a decrease in inhibition measured by TMS over the motor cortex following atomoxetine administration [18]. Furthermore, Sczesny-Kaiser et al. showed that application of excitatory high-frequency rTMS over the primary motor cortex combined with atomoxetine treatment acted synergistically to enhance motor cortical excitability and motor learning in healthy subjects [19]. The results of the above studies suggest that the concomitant use of atomoxetine seems to facilitate functional recovery induced by other rehabilitative approach in patients with brain diseases, through the enhancement of brain plasticity. As discussed above, there are no previous studies on the effects of atomoxetine when administered with other rehabilitative approaches in post-stroke patients.

In a series of studies, we demonstrated the therapeutic effects of rTMS and OT for post-stroke upper limb hemiparesis [20–22]. Currently, more than 1000 stroke patients have received the combination of rTMS and OT across

Japan, and the clinical results of the treatment are favorable. The combination of rTMS and OT is generally safe and can significantly improve motor function in the affected upper limb. The underlying mechanism of the effect of rTMS is mainly functional reorganization in the lesional hemisphere, since suppressive low-frequency rTMS over the non-lesional hemisphere reduces interhemispheric inhibition toward the lesional hemisphere and indirectly activates the lesional hemisphere [27]. Serial functional MRI imaging and motor tasks showed that rTMS/OT over 15 days produced significant neural reorganization in the lesional hemisphere [28]. Based on these findings, we postulated that atomoxetine treatment can produce further enhancement of brain plasticity and reorganization in the lesional hemisphere when combined with rTMS/OT, and thus better functional recovery of upper limb motor function. To our knowledge, this is the first clinical report that describes the therapeutic use of atomoxetine combined with rTMS and OT for post-stroke patients.

Motor functional improvement in the affected upper limb was noted in all the patients. Since no neuroimaging, such as functional MRI or PET, in this study, the exact mechanism for the improvement remains elusive. However, we speculate that atomoxetine enhanced the positive effects of low-frequency rTMS/OT on brain plasticity, producing functional recovery of motor function in the affected upper limb. This enhancement of brain plasticity may lead to further beneficial plastic change in the lesional hemisphere. It is possible that the concomitant application of two interventions (atomoxetine and rTMS) provides an “enriched environment” for functional recovery after stroke. We recommend aggressive rehabilitation with some interventions designed to enhance brain plasticity, once safety of the interventions is confirmed. Especially, we suggest that treatment of post-stroke symptoms with atomoxetine should be encouraged to “condition” the brain to be more responsive to other interventions. The safety and feasibility of the protocol seem acceptable, since it was tolerated by three patients. We consider the inclusion criteria used in this study were appropriate, although they may seem to be relatively strict for real clinical settings of stroke.

This study has certain limitations. First, this is a pilot study of only three post-stroke patients. Therefore, the safety and efficacy of this combination protocol should be confirmed in a larger number of patients. Second, the design of this pilot study did not allow evaluate the separate effect of each component of the combination protocol. Further studies to assess this issue are needed, with serial application of functional neuroimaging if possible. Third, the follow-up period of 4 weeks is relatively short and longer period is needed to determine the duration of motor function improvement.

Conclusion

In this pilot study, we demonstrated the safety and clinical benefits of the triple-element protocol featuring oral atomoxetine, rTMS, and OT in three post-stroke hemiparetic patients. The findings suggest that atomoxetine synergistically enhances the functional recovery of motor function following 15-day dual therapy of rTMS and OT.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

Ethical approval The study protocol and intervention were approved by the ethics committee of our university.

Informed consent Informed consent was obtained from the all of three patients.

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