

ORIGINAL**Clinical Uses of a Robot (Hybrid-Assisted Limb or HAL™) in Patients with Post-stroke Spasticity after Botulinum Toxin Injections**Tsuyoshi Okuno^{1, 2}, Toshiaki Takeuchi^{2, 3}, Eiji Takeda¹, Yuisin Izumi², and Ryuji Kaji^{2, 3}¹*Kenshokai Gakuen College for Health and Welfare, Tokushima, Japan*, ²*Department of Neurology, Tokushima University, Tokushima, Japan*,³*Department of Neurology, Utano National Hospital, Kyoto, Japan*

Abstract: Spasticity is the major cause of disabilities in stroke-survivors. Botulinum neurotoxin (BoNT) injections have been used to reduce the muscle tone in those patients, but its efficacy in functional outcome is not well delineated. We have studied the effect of a robot (Hybrid-Assisted Limb or HAL™) designed for assisting the elbow flexion and extension in those who underwent BoNT injections with reduced muscle tone. We enrolled 15 post stroke patients who had BoNT injections for more than 12 months. They were measured for active ROM (range of motion) with video recordings before and after the use of HAL for 40 minutes. Active ROM was measured by a rater who were blinded as to the use of the robot. Significant increase of active ROM was observed immediately after the use of HAL, and the effect was maintained for another 12 months by repeating the sessions. It is suggested from present study that the combined use of BoNT and robotics is effective efficacious for regaining the active function of the upper limb in stroke survivors. *J. Med. Invest.* 68: 297-301, August, 2021

Keywords: Stroke, spasticity, botulinum, robotics, hybrid-assisted limb

INTRODUCTION

Paralysis of the upper limbs is seen in up to 85% of stroke survivors (1), and 25% of them develop total loss of the function of the limb by 5 years after the stroke onset (2). Among those survivors, it has been estimated that 38% of them suffer from spasticity (3). According to the estimation of Japanese government in 2017, the number of those stroke survivors in Japan amount to 1.2 million, and those with total loss of the upper limb function are 0.3 million. Thus those disabilities cause the loss of independence in activities of daily life, lack of self-esteem of those survivors and the increased burden of care in the society. It would be desirable to find a method for those with upper limb disability to regain its active function in order to reduce not only the cost of care in Japan but also the global burden of disease (4).

Botulinum neurotoxins (BoNTs) have been approved for spasticity treatment in many countries. There is strong evidence that they reduce muscle tone in spasticity (5, 6), but it is uncertain whether they are useful in improving functional disabilities of the limbs such as increasing active range of motion (ROM). Spasticity is defined as increased muscle tone as a consequence of upper motor neuron dysfunction or loss. Since it develops later in the course of acute stroke that damages the upper motor neuron, there seems to be a maladaptive synaptic plasticity at multiple levels including the spinal cord (7). BoNTs have been shown to have direct central action after its injection into the muscle (8), and it could regain active function of the limb if combined with measures that influences the synaptic plasticity.

Robotic have been used for neurorehabilitation, and Hybrid-Assisted Limb (HAL®, Cyberdyne Co Ltd., Japan) is now being approved for spinal cord injury in many countries. The

latter is designed to pick up electrical signals in the muscle to contract, and to mechanically assist the joint to move as desired without time delay. It utilizes the principle of paired associative stimulation (PAS) (9), which links the desire to move and the actual movement evoked proprioceptive feed-backs, resulting in plastic changes (10).

We planned the object of this study into investigate whether the combination of BoNT injection and robot rehabilitation using HAL could increase active ROM compared to the effect of single BoNT injections (11).

SUBJECTS

We screened 35 patients with post-stroke spasticity who had been treated with BoNT injections for more than 12 months (or 3-4 sessions of 200-300 units of onabotulinumtoxinA). After excluding those who could not accept the purpose of the study and were not adaptable to the robot (n = 10), we enrolled 25 patients for the study period, after obtaining informed consent. Those who were unable to visit regularly for the robot therapy or BoNT injections (n = 10) were also eliminated. Total of 15 patients were analyzed (Fig. 1). Baseline characteristics of the patients are shown in Table 1.

This study was approved by the Institutional Review Board (No.2483) of the Tokushima University (Tokushima, Japan). The procedures were fully explained to subjects and an informed consent form was signed.

METHODS

The robot was a machine fitted for the elbow joint, or single-joint HAL (HAL-SJ; Fig. 2), which detects muscle activities of the elbow flexor (biceps brachii muscle) and the extensor (triceps brachii muscle). The electric signals triggered the robot arm, which instantly (<50msec) flexes or extends the elbow.

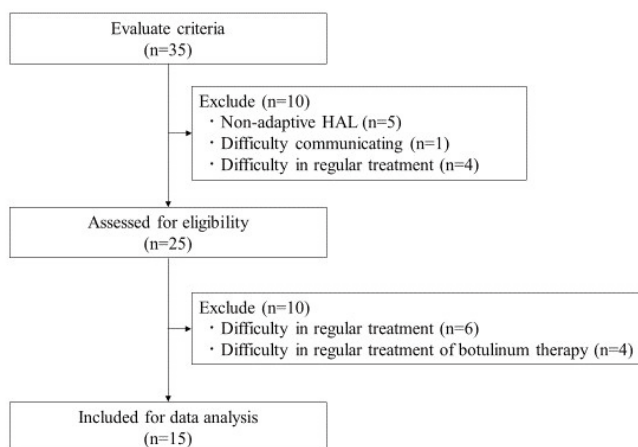
The patients were evaluated for active ROM by videotaping

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Address correspondence and reprint requests to Tsuyoshi Okuno, Kenshokai Gakuen College for Health and Welfare, 369-1 Higashi takawa, Tenma, Kokufu-cho, Tokushima, 779-3105, Japan and Fax : +81-88-642-9227.

Table 1. Baseline characteristics of the patients

Case	Age (year)	Gender	Handedness	Diagnosis	Location of lesion	Interval from onset (year)	Brunnstrom stage
1	53	Male	Right	Ischemia	Internal carotid artery (ICA) dissection	6	III
2	69	Male	Right	Ischemia	Middle cerebral artery (MCA) occlusion	9	II
3	48	Female	Right	Hemorrhage	putamen	8	II
4	69	Male	Left	Hemorrhage	putamen	8	II
5	70	Female	Right	Hemorrhage	putamen	19	II
6	60	Male	Right	Hemorrhage	putamen	11	IV
7	65	Male	Right	Hemorrhage	putamen	12	IV
8	73	Male	Left	Ischemia	Corona radiata	5	IV
9	68	Male	Right	Ischemia	Middle cerebral artery (MCA) occlusion	7	IV
10	73	Male	Left	Ischemia	Corona radiata	8	IV
11	75	Male	Left	Ischemia	Corona radiata	6	IV
12	73	Male	Right	Hemorrhage	putamen	8	IV
13	68	Female	Left	Hemorrhage	putamen	10	III
14	59	Male	Right	Ischemia	Cardioembolic	6	II
15	64	Female	Right	Ischemia	Middle cerebral artery (MCA) occlusion	7	III
Mean (SD)	65.8 (7.8)					8.6 (3.4)	

**Fig 1.** Flow diagram of patient selection.

after having BoNT injection (onabotulinumtoxinA or BOTOX® 200-300units) into muscles at the shoulder, elbow and wrist joints. Then they were fitted for HAL-SJ, and had a series of test runs for 10-15 minutes to confirm that the machine flexes or extends the elbow at the patient's will. After these tests, they had 40 minutes session of the elbow joint movement training assisted by HAL-SJ. Before and immediately after these sessions, the patients were assessed for active ROM of the elbow joint by videotaping. Additional evaluation was made as to modified Ashworth Scale (MAS) of the elbow joint, and Fugl-Meyer Assessment (FMA; Upper Extremity-A items; range 0-36). The same procedure was repeated at each of the following 4 sessions of 3 months interval (12 months), and all active ROM of the elbow joint were taped for *post hoc* review by a rater blinded as to the timing of HAL intervention.

The assessment schedule is depicted in Fig. 3. The changes of active ROM between 12 months before and immediately before starting HAL rehabilitation (0 month) were assessed as Baseline, reflecting only the effects of BoNT injections without HAL.

At 0 month, HAL was tried immediately after BoNT injection, when BoNT effects were not apparent (HAL-SJ). At 1 month after the initial HAL training, when the BoNT effects were supposed to be maximum, HAL training session was repeated as HAL+BTX, which indicates the combined effects of BoNT and HAL for a single session. At 6 months, HAL was repeated with assessment (6mo), which mirrors the effect of 2 times of BoNT injections and 4 HAL sessions. At 12 months after the start (1yr), assessment was made immediately after HAL training, reflecting 4 times of BoNT sessions and 6 times of HAL trainings. The subjects received the occasional rehabilitation (usually 40 minutes/week) during the entire test period, and its protocol was not changed.

All statistical analyses were performed using EZR (12). EZR is a modified version of R commander designed to add statistical

**Fig 2.** The single-joint Hybrid Assistive Limb(HAL-SJ). The controller showing the Bioelectrical signals.

functions frequently used in biostatistics. In addition, changes in ROM were assessed with Bonferroni correction, MAS and FMA were assessed with paired t-test and Wilcoxon's signed-rank test. For all outcome variable, the critical value for rejection of the hypothesis set at $P < 0.05$. The effect size (d) was established by calculating the difference between the means of the experimental and control groups divided by the average population standard deviation. The effect size was based on the classification of Cohen, it is classified as small ($d \geq 0.2$), medium ($d \geq 0.5$), and large ($d \geq 0.8$).

RESULTS

The changes of active ROM in each patient is depicted in Fig.4. The effect of HAL was apparent immediately after the session (HAL-SJ ; $p < 0.05$, Bonferroni correction), but the effect size (d) was small (Table 2). After completing the combined BoNT and HAL interventions for a year (1-Year), active ROM increased from $49.0 \pm 33.7^\circ$ to $63.3 \pm 37.1^\circ$, which was significant after multi-variance analysis ($p < 0.05$), and the effect size was medium. The other functional outcome, FMA-UE improved from 12.1 ± 3.9 to 14.6 ± 5.4 , a significant increase (Table 3, $p < 0.01$,

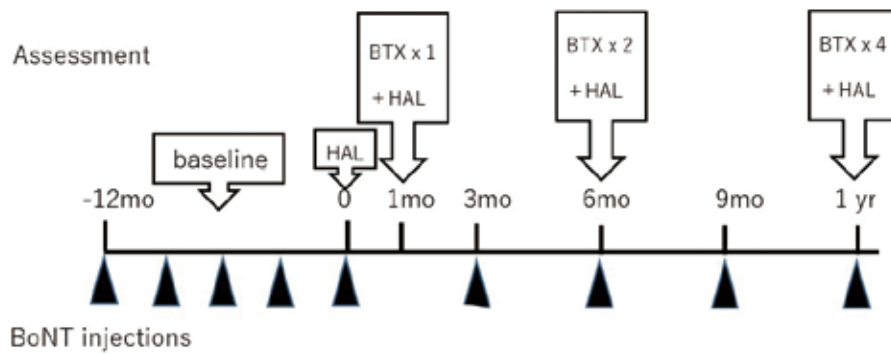


Fig 3. Summary of the patient's clinical course.

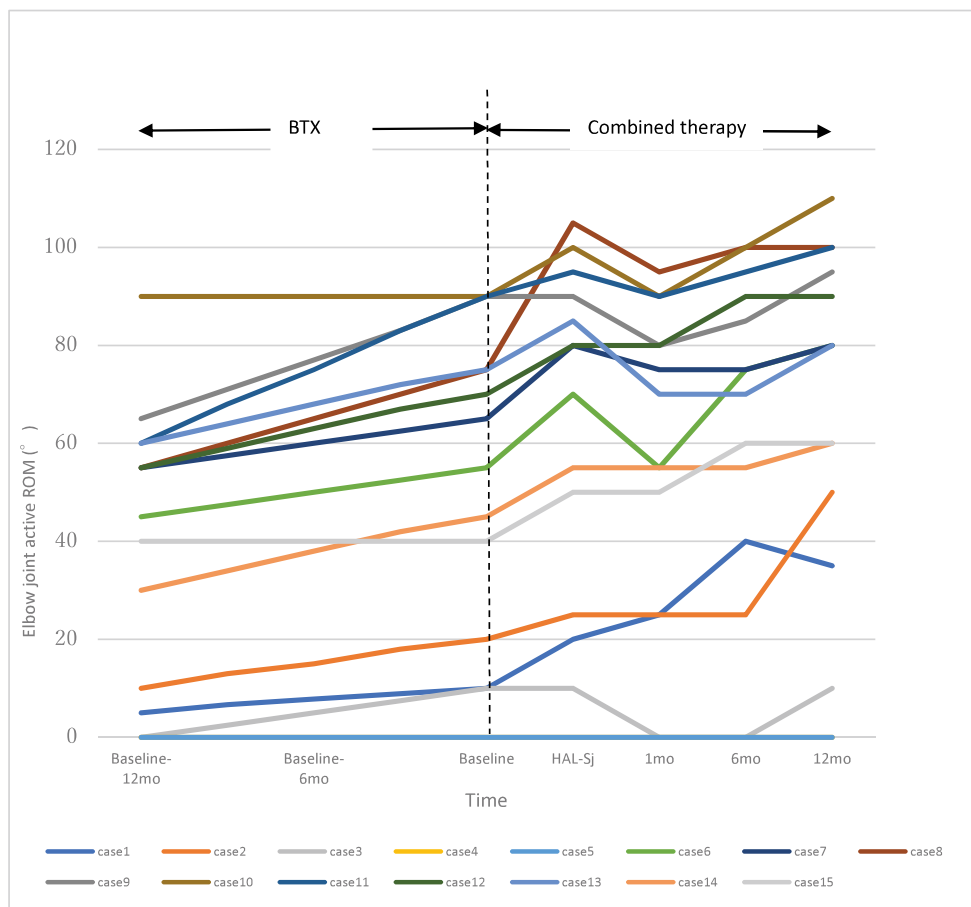


Fig 4. Active range of joint motion change of elbow for 2 years.

Table 2. Active range of motion change of elbow and comparison with baseline

n	Elbow jt	-12month	Baseline	HAL-SJ	1month	6month	12month
15	ROM (°)	38.0 (28.8)	49.0 (33.7)	57.7 (37.6)	52.7 (34.6)	58.0 (36.7)	63.3 (37.1)

Outcomes		case (n = 15)		
		-12month	HAL-SJ	12month
Baseline	Active ROM	P = 0.0217*	P = 0.0194*	P = 0.0146*
	Effect size	0.382	0.257	0.425

*Bonferroni correction (Multi-variance analysis)
Effect size(d) = 0.20(small), 0.50(medium), 0.80(large)

Table 3. Changes in functional outcomes

Outcomes		Baseline Mean (SD)	Baseline+1year Mean (SD)	P value
Fugl-Meyer Assessment	Proximal	12.1 (3.9)	14.6 (5.4)	P=0.001*
Modified Ashworth Scale	Elbow-flexor	1.6 (0.3)	1.4 (0.4)	P=0.047**

*Wilcoxon rank-sum test **Paired t-test

paired-t test). It is however noted that the changes of active ROM was also significant during the period of 1 year before the start of HAL using only BoNT injections ($38.0 \pm 28.8^\circ$ to $49.0 \pm 33.7^\circ$). MAS slightly improved from 1.6 ± 0.3 to 1.4 ± 0.4 (Table 3, $p < 0.05$, Wilcoxon rank-sum test).

DISCUSSION

The present study clearly demonstrated immediate beneficial effects on active ROM of robot rehabilitation using HAL in those patients who had undergone BoNT injections previously. If the joint was rigid by severe spasticity, it would not have been possible to use HAL because of its mechanical limitations to safety. It is therefore clear that the combination of BoNT and HAL could increase the active function of the limb. It's long term effects were also supported at 1 year considering the effect size, but it is not clear whether the combination therapy was superior to BoNT injections with conventional rehabilitation alone.

The mechanism of spasticity has been explored in the past, but its precise mechanism is not fully understood. Spasticity is a syndrome of increased muscle tone caused by upper motor neuron dysfunction with exaggerated deep tendon reflexes (13, 14), but the acute loss of upper motor neuron does not cause spasticity. Spasticity develops after sometime in the course of stroke convalescent period. Therefore it appears that maladaptive synaptic plasticity at least in the spinal cord may be the key factor for its development. BoNT injections influences central synapses directly or indirectly (8), and may rectify the abnormal neuroplasticity at the spinal cord level.

Paired-associative stimulation (PAS) is a well-established physiological phenomenon (15). It refers to a paradigm consisting of repetitive median nerve stimulation combined with transcranial magnetic stimulation (TMS) over the contralateral motor cortex. This protocol has been shown to induce plastic changes of excitability in the brain, and its presumed mechanisms include long-term potentiation (LTP), a cellular mechanism likely to be relevant for learning and memory. Of particular importance is

the fact that PAS-induced changes of the size of amplitudes of the motor evoked potentials (MEPs) depends on the exact interval between the afferent and the magnetic pulse during the intervention.

The mechanism of the immediate effect of HAL in the present study seems to be similar to PAS: the intention to move the joint, a self-initiated cortical stimulation, is combined without time delay with the actual movement perceived through the proprioceptive input back to the cortex, possibly resulting in LTP at the cortical level. Since the stroke patients do not have normal upper motor neurons at the primary motor cortex, the magnetic stimulation over the diseased cortices is not feasible. The limb movement-induced inputs to the remaining cortices by utilizing HAL would be more practical than the transcranial magnetic stimulation (10, 11).

In conclusion, the present study demonstrated immediate effects of improving active ROM of the elbow joint in patients with decreased spasticity due to stroke who had had BoNT injection for more than 1 year. Its long-term effects were promising in further ameliorating the active function of the limb.

CONFLICT OF INTEREST

The authors have no conflict of interest declare.

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