Clinical Uses of a Robot (Hybrid-Assisted Limb or HAL™) in Patients with Post-stroke Spasticity after Botulinum Toxin Injections

Tsuyoshi Okuno1, 2, Toshiaki Takeuchi2, 3, Eiji Takeda1, Yuisin Izumi2, and Ryuji Kaji2, 3

1Kenshokai Gakuen College for Health and Welfare, Tokushima, Japan, 2Department of Neurology, Tokushima University, Tokushima, Japan, 3Department 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...
Effects of BTX and Robot (HAL)

After having BoNT injection (onaabotulinumtoxinA 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 minues 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 joints 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

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             | V               |
| 9    | 68         | Male   | Right      | Ischemia  | Middle cerebral artery (MCA) occlusion | 7             | V               |
| 10   | 73         | Male   | Left       | Ischemia  | Corona radiata   | 8             | V               |
| 11   | 75         | Male   | Left       | Ischemia  | Corona radiata   | 6             | V               |
| 12   | 73         | Male   | Right      | Hemorrhage | putamen          | 8             | V               |
| 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)
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 $12.1 \pm 3.9$ to $14.6 \pm 5.4$, a significant increase (Table 3, $p < 0.01$, Fig. 3. Summary of the patient’s clinical course.

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

Fig 4. Active range of joint motion change of elbow for 2 years.
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±28.8° to 49.0±33.7°). 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. Its 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 in the spinal cord is the key factor for its development. BoNT injections influence 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.

**ACKNOWLEDGEMENTS**

The authors thank the study participants and members of our laboratory, the staff of Kenshokai Gakuen.

**REFERENCES**

1. Skilbeck CE, Wade DT, Hewer RL, Wood VA: Recovery after stroke. J Neurol Neurosurg and Psychiatry 46: 5-8, 1983
2. Geddes JM, Fear J, Tennant A, Pickering A, Hillman M, Chamberlain MA: Prevalence of self-reported stroke in a population in northern England. J Epidemiol Community Health 50: 140-143, 1996
3. Watkins CL, Leathley MJ, Gregson JM, Moore AP, Smith TL, Sharma AK: Prevalence of spasticity post stroke. Clin Rehabil 16: 515-522, 2002
4. Kaji R: Global burden of neurological diseases highlights stroke. Nature Reviews Neurology 15: 371-372, 2019
5. Kaji R, Osako Y, Suyama K, Maeda T, Uechi Y, Iwasaki M, Group GSKSS: Botulinum toxin type A in post-stroke upper-limb spasticity. Current Medical Research Opinion 26: 1983-1992, 2010
6. Masakado Y, Abo M, Kondo K, Saeki S, Saitoh E, Dekundy A, Hanschmann A, Kaji R, Group JPS: Efficacy and safety of incobotulinumtoxinA in post-stroke upper-limb spasticity in Japanese subjects: results from a randomized, double-blind, placebo-controlled study (J-PURE). Journal of Neurology 267: 2029-2041, 2020
7. Filli L, Schwab ME: Structural and functional reorganization of propriospinal connections promotes functional recovery after spinal cord injury. Neural Regeneration Research 10: 509-513, 2015
8. Kaji R: Direct central action of intramuscularly injected botulinum toxin: is it harmful or beneficial?. The Journal of Physiology 591: 749, 2013
9. Silverstein J, Cortes M, Tsagaris KZ, Climent A, Gerber LM, Oromendia C, Fonziotti P, Ratan RR, Kitago T, Iacoboni M, Wu A, Dobkin B, Edwards T: Paired Associative Stimulation as a Tool to Assess Plasticity Enhancers in Chronic Stroke. Frontiers in Neuroscience 13: 792, 2019
10. Saita K, Morishita T, Arima H, Hyakutake K, Ogata T, Yagi K, Shiota E, Inoue T: Biofeedback effect of hybrid assistive limb in stroke rehabilitation: A proof of concept study using functional near infrared spectroscopy. PLoS One 13: e0191361, 2018
11. Saita K, Morishita T, Hyakutake K, Fukuda H, Shiota E, Sankai Y, Inoue T: Combined therapy using botulinum toxin A and single-joint hybrid assistive limb for upper-limb disability due to spastic hemiplegia. Journal of the Neurological Sciences 373: 182-187, 2017
12. Kanda Y: Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant 48: 452-458, 2013
13. Lance JW: What is spasticity?. The Lancet 335: 606, 1990
14. Lance JW, Burke D: Mechanisms of spasticity. Archives of Physical Medicine and Rehabilitation 55: 332-337, 1974
15. Joseph C, Alexander W, Katja S, Matthias W, Friedhelm S, Arne S, Erwin K: Paired associative stimulation. Supplements to Clinical Neurophysiology 57: 563-569, 2004