INTRODUCTION
Persistent functional deficit in the arm is a serious concern for stroke patients. Treatment of such functional deficit is critically important for stroke rehabilitation, because approximately 15%-30% of stroke survivors experience long-lasting paresis in the affected arm. For such patients, botulinum toxin type A (BtxA) injection combined with arm motor rehabilitation offers a promising approach to enhance recovery after stroke.

Robotic therapy (RT) has recently proved effective in patients with moderate and severe arm weakness after stroke. However, some researchers have reported that using robotics alone does not promote use of the affected arm in activities of daily living (ADL) [1]. Meanwhile, constraint-induced movement therapy (CIMT) has also been applied and has proved effective in various randomized controlled trials. CIMT has been shown to considerably improve the function and amount of use of the paretic arm in ADL when administered in chronic stroke patients with mild-to-moderate motor deficits [2,3]. A key limitation of CIMT is the strict minimal inclusion criteria, namely, the ability to extend the metacarpophalangeal and interphalangeal joints by at least 10° and the wrist joint by at least 20°. However, recent studies of CIMT have examined and allowed the use of adaptive approaches for stroke patients with severe paresis to achieve the minimal inclusion criteria for starting CIMT. Such approaches are designed to compensate the patient for the lack of arm function, particularly voluntary extension of the paretic fingers [4].

BtxA injection, RT, and CIMT are each promising approaches to enhance arm function recovery after stroke [5]. However, combined use of these procedures to compensate for their individual imperfections has not been studied.

In this report, we present a case in which we intentionally used a combination of BtxA injection and RT to facilitate CIMT with adaptive approaches, and examined whether this combined approach would both improve arm function and increase the amount of real-world use of the affected arm for ADLs in a patient with severe spastic hemiparesis.

Case Presentation

Therapeutic Synergism in the Treatment of Post-stroke Arm Paresis Utilizing Botulinum Toxin, Robotic Therapy, and Constraint-induced Movement Therapy

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Botulinum toxin type A (BtxA) injection, constraint-induced movement therapy (CIMT), and robotic therapy (RT) each represent promising approaches to enhance arm motor recovery after stroke. To provide more effective treatment for a 50-year-old man with severe left spastic hemiparesis, we attempted to facilitate CIMT with adaptive approaches to extend the wrist and fingers using RT for 10 consecutive weeks after BtxA injection. This combined treatment resulted in substantial improvements in arm function and the amount of arm use in activities of daily living, and may be effective for stroke patients with severe arm paresis. However, we were unable to sufficiently prove the efficacy of combined treatment based only on a single case. To fully elucidate the efficacy of the combined approach for patients with severe hemiparesis after stroke, future studies of a larger number of patients are needed.

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Teijin Pharma Ltd. (Tokyo, Japan) loaned the robotic system to the authors at no charge to evaluate the effects of the robotic therapy.

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CASE PRESENTATION

The patient was treated at the Hospital of Hyogo College of Medicine from February 2012 to May 2012. He was a 50-year-old man who had a history of infarction of the right frontal cortex and internal capsule 24 months before the intervention. After stroke onset, the patient had received 2 hours of standard inpatient rehabilitation every day for 6 months. After discharge from the hospital, he received 2 hours of daily standard rehabilitation in a welfare facility. After being discharged from the welfare facility, he had received 1 hour of standard outpatient rehabilitation once a week for 12 months before this study. This regimen was possible because of the rehabilitation system in Japan. The Japanese medical insurance system allows patients with stroke to receive inpatient rehabilitation for 6 months and outpatient rehabilitation for approximately 4 hours per month beyond 6 months after the stroke event. In addition, Japanese law for the welfare of individuals with physical disabilities allows patients with severe hemiparesis after stroke to receive rehabilitation every day in a welfare facility for months 7-12 after the stroke event if permitted by their physician.

During the study, the patient did not receive any other ambulatory rehabilitation from other clinics or hospitals. No cognitive deficits were noted in the patient. At screening, he was not able to extend the affected fingers at all, but was able to flex them. He had achieved full independence in basic ADL using only the unaffected arm, and reported not using the affected arm for any ADL.

From 1 week after BtxA injection, the patient received 1 hour of RT and 0.5 hour of CIMT with adaptive approaches 3 times per week for 10 consecutive weeks. The goals that the patient set for himself were to: 1) hold vegetables with the affected arm while cutting them with a kitchen knife; 2) open/close a door with the affected arm; and 3) use a broom or scrubbing brush with both arms. The ethics committee of our university approved the treatment protocol, and informed consent was obtained from the patient.

Methods

The patient received injection of 240 units of BtxA (Botox; Glaxo Smith Kline, Tokyo, Japan) to allow active and passive extension of the elbow, wrist, and fingers. BtxA supplied as a vacuum-dried powder in a 100-unit vial was reconstituted with 2 mL of sterile saline solution (0.9%) to obtain a concentration of 50 units/mL. The muscle belly of the biceps

Figure 1. The device used for robotic therapy. (A) Outward appearance of the ReoGo system. (B) Use of a display in training. (C-E) The support grip for the arm can be varied according to arm function and the physical condition of the patient.
The brachii muscle was injected with 40 units. The flexor digitorum superficialis, flexor digitorum profundus, flexor carpi ulnaris, and flexor carpi radialis muscles were each injected with 50 units.

We used the Reo Therapy System (ReoGo; Motorika Medical, Caesarea, Israel) (Figure 1) for RT. Teijin Pharma (Tokyo, Japan) loaned the robotic system to us at no charge for evaluation of the effect of RT. ReoGo is a robotic system for comprehensive arm therapy, designed to facilitate repetitive multi-directional arm movements, and offering 5 levels of assistance from total assistance to total voluntary modes. ReoGo has a motorized robotic arm (stick) with a platform for stabilizing the subject’s forearm to assist in arm movement. The patient was instructed to move the stick for point-to-point reach tasks. The distance, direction, and degree of robotic-assisted reach movements were adjusted in small steps of progressively increasing difficulty according to the arm function and physical condition of the patient. ReoGo provided visual and auditory feedback to the success of reaching movements by the subject.

The CIMT protocol involves 3 main elements: (1) repetitive, task-oriented training of the affected arm, approached in small steps of progressively increasing difficulty to suit the arm function and physical condition of the patient; (2) “Transfer Package,” designed to facilitate transfer of therapeutic gains made in clinical settings to real-world activities; and (3) restraining the unaffected arm to promote use of the affected arm [3]. We modified this protocol by decreasing the amount of time and frequency of training. In addition, we modified the Transfer Package to fit the clinical setting of our hospital, and its efficacy and validity have previously been reported [2].

Furthermore, we used adaptive approaches to compensate for the lack of arm function in stroke patients with severe hemiparesis to achieve the minimal inclusion criteria for starting CIMT. These adaptive approaches comprised neuromuscular electrical stimulation (NMES) and orthotics, to assist in voluntary finger extension during the task-oriented training in CIMT. We used the NMES system (MURO Solution; Pacific Supply, Osaka, Japan) to supply “integrated volitional control electrical stimulation” [6], which continually changes the stimulation intensity in direct proportion to the amplitude of voluntary electromyograms and applies electrical stimulation of sub-threshold motor intensity. The MURO Solution is a portable, noninvasive (surface) electromyogram serving as a controlled, single-channel neuromuscular electrical stimulator (Figure 2A). Arm and finger orthotics were used to assist voluntary pinch grip and finger extension.

Figure 2. Neuromuscular electrical stimulation device and orthotics during constraint-induced movement therapy. (A) Neuromuscular electrical stimulation (NMES) device, which is placed on the extensor of the paretic finger (extensor digitorum muscle) to assist in voluntary finger extension. A pair of electrodes for electromyography detection and stimulation were placed 5 mm apart on the proximal position of the affected extensor digitorum muscle. The other electrode for reference and stimulation was placed on the distal position of the affected extensor digitorum muscle. Biphasic square waves were applied at 20 Hz for 300 μs. (B) Dorsal cock-up wrist splint, short opponent splint, and dynamic splint, termed the “spider splint.” The dynamic splint is made with memory metals and has 4 bridges between the thumb and second to fifth fingers on the dorsum of the hand, reinforcing the powers of the second to fifth fingers in extension and the thumb in abduction.
extension and included a dorsal cock-up wrist splint, a short opponens splint, and a dynamic splint similar to a spider splint [7], as used in patients with radial paralysis (Figure 2B). We encouraged the patient to use these supportive devices in actual ADL.

For outcome assessments of the trained paretic arm, we used the Fugl-Meyer Assessment for the upper extremity (FMA) [8], the Wolf Motor Function Test (WMFT) [9], the Motor Activity Log (MAL) [10] active/passive range of motion (ROM), the Motoricity Index [11], and the Modified Ashworth Scale (MAS) [12] both before and after intervention. The FMA assesses paretic arm function in stroke patients. We used all 30 items on basic arm function (movements and reflexes of the shoulder, elbow, forearm, wrist, and hand) and 3 items on coordination and speed. The WMFT consists of 15 activities items and assesses performance of the affected arm. The test has 2 components, in the form of qualitative (functional ability scale) and temporal (time in seconds) assessments. The MAL is a questionnaire-structured interview surveying 14 activities of daily living. The test comprises 2 subscales for rating the affected arm in real-life situations: an amount-of-use scale and a quality-of-movement scale. The Motoricity index assesses the strength of the paretic shoulder, elbow, and finger in the stroke patient. The MAS assesses muscular tone (muscle spasms) during passive joint movements. The outcome ranges for each assessment are shown in the legend to Table 1. Assessments were made by trained occupational therapists who were not involved in the present case presentation.

Outcomes

All outcome measures improved substantially after the intervention (Table 1). After the intervention, the patient was able to hold (pinch) and release objects using the affected fingers without the support of adaptive approaches, because he was voluntarily able to extend the affected fingers. Moreover, he accomplished all of the goals that he set at the beginning of the study.

DISCUSSION

This case report describes the combined application of BtxA injection and RT to facilitate CIMT with adaptive approaches in a chronic stroke patient with severe arm paresis. We intentionally incorporated these different treatment strategies to compensate for each one’s limitations. BtxA can allow the patient to achieve the minimal criteria for CIMT and promote the repetitive arm training needed in RT and CIMT. Meanwhile, repetitive arm training (in RT and CIMT) is able to reduce spasticity [13]. We believe that these 3 different treatments can thus act synergistically to improve arm function.

In this case presentation, our intervention promoted not only the function but also the use of affected arm in ADL. A 6- to 7-point increase in FMA [14] and 40% increase in MAL [15] are defined as clinically meaningful changes. The improvements in both FMA and MAL in the present case were greater than these thresholds for clinically meaningful change, and treatment was thus considered clinically effective.

In recent years, BtxA injection has been shown to be effective for decreasing spasticity in the affected arm after stroke. However, guidelines for the use of botulinum toxin in the management of adult spasticity [16] recommend the use of BtxA injection as part of a rehabilitation program. This means that the reduction of spasticity is not in itself sufficient to increase arm function. The present case presentation supports a recent study by Sun et al [17] that described BtxA and arm motor training administered consecutively to stroke patients, resulting in functional gains for the affected arm.

Previous studies have shown that RT alone improved function (as measured by FMA) better than conventional rehabilitation, but did not improve use of the affected arm (as measured by MAL) [18,19]. In the present report, the patient was trained using CIMT with adaptive approaches in addition to RT, and showed improvements on both FMA and MAL. This might be attributable to the behavioral approach of CIMT called the Transfer Package, which aims

### Table 1. Affected arm function before and after intervention

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fugl-Meyer Assessment</td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td>Wolf Motor Function Test</td>
<td>80.81</td>
<td>65.2</td>
</tr>
<tr>
<td>Performance time (s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional ability scale</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Motor Activity Log</td>
<td>0.58</td>
<td>1.13</td>
</tr>
<tr>
<td>Amount of use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of movement</td>
<td>0.58</td>
<td>1.08</td>
</tr>
<tr>
<td>Active/passive range of motion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder flexion</td>
<td>70 / 140</td>
<td>130 / 150</td>
</tr>
<tr>
<td>Shoulder abduction</td>
<td>75 / 135</td>
<td>105 / 150</td>
</tr>
<tr>
<td>Elbow extension</td>
<td>90 / 130</td>
<td>150 / 150</td>
</tr>
<tr>
<td>Forearm pronation</td>
<td>90 / 90</td>
<td>90 / 90</td>
</tr>
<tr>
<td>Forearm supination</td>
<td>-5 / 60</td>
<td>5 / 60</td>
</tr>
<tr>
<td>Wrist extension</td>
<td>-5 / 50</td>
<td>5 / 70</td>
</tr>
<tr>
<td>Motricity Index (strength)</td>
<td>18.67</td>
<td>34.33</td>
</tr>
<tr>
<td>Modified Ashworth Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbow</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Wrist</td>
<td>2</td>
<td>1+</td>
</tr>
<tr>
<td>Finger</td>
<td>2</td>
<td>1+</td>
</tr>
</tbody>
</table>

Scores for the Fugl-Meyer Assessment for the arm component range from 0 (severe paresis) to 66 (normal). The Functional Ability scale of the Wolf Motor Function Test is a 6-level scale from 0 (does not attempt with the involved arm) to 5 (movement appears to be normal). Performance time for the Wolf Motor Function Test is also recorded for each movement item (from 0 to 120 seconds). Scores for the Motor Activity Log range from 0 (no use) to 5 (normal use). Normal active/passive range of motion values for the upper limb movements: shoulder flexion, 0°–180°; shoulder abduction, 0°–180°; elbow extension, 150°–0°; forearm pronation/supination, 0°–90°; and wrist extension, 0°–70°. Scores for the Motoricity Index range from 0 (cannot contract) to 100 (normal strength). The Modified Ashworth scale uses a 6-grade scale: 0, no increase in muscle tone; 1, 1++; 2, 2; 3, and 4, the affected part is rigid in both flexion and extension.
to increase the amount of use of the affected arm under real-life circumstances.

In a clinical setting, we were able to combine multiple therapeutic modalities (BtxA, RT, NMSE, splint) to facilitate CIMT and, in turn, to improve arm function in a stroke patient with hemiparesis. Therapists are encouraged to treat patients with severe hemiparesis using a combination of different types of interventions as part of a comprehensive approach. Each treatment used in the present case has been established as an effective treatment, and our combined approach synergistically afforded successful results. However, we were unable to confirm the long-term efficacy of this combined therapy. To fully elucidate the long-term efficacy of such an approach, long-term follow-up studies are needed. In addition, we were unable to sufficiently prove the efficacy of combined treatment with BtxA injection, RT, and CIMT with adaptive approaches based on only a single case. To fully elucidate the efficacy of the combined approach for patients with severe hemiparesis after stroke, future studies of a larger number of patients are needed. Considering the promising outcome seen in this case, we believe that this combined approach offers promise for effectively improving arm function and the amount of arm use in ADL for stroke patients with severe paresis of the arm.

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