Neurorehabil Neural Repair OnlineFirst, published on September 3, 2009 as doi:10.1177/1545968309341060

Neurorehabilitation and
Neural Repair
XX(X) xx–xx

DOI: 10.1177/1545968309341060
http://nnr.sagepub.com
SAGE

Combined Botulinum Toxin Type A With Modified Constraint-Induced Movement Therapy for Chronic Stroke Patients With Upper Extremity Spasticity: A Randomized Controlled Study

Shu-Fen Sun, MD,[1,2] Chien-Wei Hsu, MD,[2] Hsien-Pin Sun, MD,[3,4] Chiao-Wen Hwang, MD,[2] Chia-Lin Yang, and Jue-Long Wang, MD[2]

Abstract

Background and objective. Botulinum toxin type A (BtxA) injection and modified constraint-induced movement therapy (mCIMT) are both promising approaches to enhance recovery after stroke. The combined application of these 2 promising modalities has rarely been studied. The aim was to investigate whether combined BtxA and mCIMT would improve spasticity and upper extremity motor function more than BtxA plus conventional rehabilitation in chronic stroke patients with upper extremity spasticity. *Methods*. In a prospective, randomized controlled, observer-blinded trial with 6-month follow-up, 32 patients (≥1 year after stroke) with ability to actively extend >10° at metacarpophalangeal and interphalangeal joints and 20° at wrist of the affected upper limb were randomized to receive BtxA + mCIMT (combination group) or BtxA + conventional rehabilitation (control group) for 2 hours/day, 3 days/week for 3 months. The primary outcome assessed spasticity on the Modified Ashworth Scale. Secondary outcomes assessed real-world arm function (Motor Activity Log), laboratory motor activity (Action Research Arm Test), and patients' global satisfaction. *Results*. A total of 32 stroke patients were recruited, and 29 completed the study. Spasticity significantly improved in all subjects at 4 weeks and 3 months postinjection without between-group differences. The combination group showed significantly greater improvements in elbow, wrist, and finger spasticity ($P = .019$, $P = .019$, and $P < .001$, respectively), affected upper extremity real-world arm function ($P < .001$) and laboratory motor activity ($P < .001$) than the control group at 6-month postinjection. Patients reported considerable satisfaction and no serious adverse events occurred. *Conclusions*. Combining BtxA and mCIMT is an effective and safe intervention for improving spasticity and motor function in chronic stroke patients. The results are promising enough to justify further studies. We recommend future research to address the likely need for including rehabilitation with BtxA to improve function in patients with poststroke spasticity.

Keywords

botulinum toxin, constraint-induced movement therapy, spasticity, stroke, rehabilitation

Introduction

Significant spasticity and impaired manual dexterity are often among the most disabling motor symptoms after stroke. Despite improvements in the management of stroke patients, one-third of patients are left with a nonfunctioning or partially functioning arm often with prominent spasticity.[1] In recent years, botulinum toxin type A (BtxA) has been shown to be safe and effective in the treatment of upper extremity spasticity after stroke.[2-5] However, spasticity reduction alone is not guaranteed to result in function gains.[6,7] A recent case report by Page et al[8] described that modified constraint-induced movement therapy (mCIMT) and BtxA administered consecutively

[1]National Yang-Ming University School of Medicine, Taiwan
[2]Veterans General Hospital, Kaohsiung, Taiwan
[3]Cheng Ching Hospital, Taiwan
[4]Feng Chia University, Taiwan

Corresponding Author:
Shu-Fen Sun, Department of Physical Medicine and Rehabilitation, Veterans General Hospital, Kaohsiung, 386, Ta-Chung 1st Road, Kaohsiung 813, Taiwan
E-mail: sfsun.tw@yahoo.com.tw

to the same stroke patient resulted in even greater function of the affected upper extremity. The authors raised the idea of increasing treatment efficacy by combining these 2 modalities.

Constraint-induced movement therapy (CIMT) and mCIMT are rehabilitative strategies used primarily with the poststroke population to increase the functional use of the affected upper extremity.[9-16] Only approximately 20% to 25% of stroke survivors who meet minimal motor criteria could benefit from CIMT and most CIMT research excluded patients with significant spasticity.[9,14-16] Besides, very few studies have addressed patients' subjective satisfaction after completing the study protocols.

BtxA injection and mCIMT are both promising approaches to enhance recovery after stroke. However, the combined application of the 2 modalities has rarely been studied. To date, only a single case report has addressed this issue.[17] Theoretically, application of a mCIMT program with intensive functional tasks practice after spasticity reduction by BtxA may improve affected upper extremity function for patients with poststroke spasticity. The aim was to investigate whether combined BtxA and mCIMT would produce greater improvements in spasticity and upper extremity function than BtxA plus conventional rehabilitation in chronic stroke patients with upper extremity spasticity. Patients' self-reported satisfaction after treatment was also recorded.

Methods

Subjects

Between February 2005 and November 2007, volunteers were recruited through advertisements placed in a rehabilitation department of a university-affiliated tertiary care medical center. A research team member screened volunteers using the following inclusion criteria: (*a*) age 18 to 80 years; (*b*) at least 1 year after a unilateral stroke; (*c*) Modified Ashworth Scale (MAS) score ≥3 in the elbow, wrist, or finger flexors[18]; and (*d*) ability to actively extend ≥10° at metacarpophalangeal and interphalangeal joints and 20° at wrist of the affected upper limb (minimal motor criteria).

Exclusion criteria included presence of fixed contractures, serious balance problems, preexisting neuromuscular diseases or uncontrolled medical conditions, significant cognitive deficits (Mini-Mental Status Examination score <24),[19] previous treatment with BtxA, neurolytic agents, or surgery for spasticity. All patients were not currently participating in any experimental studies and did not receive concomitant oral antispastic medication during the study period.

Using the above inclusion/exclusion criteria, 46 volunteers were screened. A total of 14 subjects were excluded as 10 subjects did not meet inclusion criteria and 4 met the exclusion criteria. Overall, 32 patients met all eligibility criteria. The study protocol was approved by the institutional review board and each participant signed a written informed consent. Once consent and baseline assessments were completed, patients were randomized to either the combination group or the control group using block randomization in groups of four by a study assistant who did not participate in subjects' evaluation or treatment.

Botulinum Toxin and Injection Technique

BtxA (Dysport; Ipsen Ltd, Berkshire, UK), supplied as vacuum-dried powder in a 500-unit vial, was reconstituted with 2.5 mL sterile normal saline (0.9%) to obtain a concentration of 200 units/mL. The total dosage injected per affected upper extremity was 1000 units. Muscles chosen for injection were based on previous experience with BtxA in upper limb spasticity.[5] A total of 400 units were injected into the muscle belly of biceps brachii at 2 sites (each site for 200 units), 150 units into each of the flexor digitorum superficialis, flexor digitorum profundus, flexor carpi ulnaris, and flexor carpi radialis at 1 site per muscle. The injections were done by the same physician and were placed in the motor endplate zone using anatomical landmarks as in routine electromyography.

Rehabilitation Interventions

The 2 different rehabilitation regimes were started 1 day after BtxA injection. Intervention was provided by a licensed physiotherapist and an experienced occupational therapist. To prevent unintended crossover, all patients were arranged to receive therapy at different times without opportunities to observe each other.

The training approaches implemented in the combination group included massed practice, shaping, a behavioral contract and a daily treatment diary. Massed practice involved intensive training of the affected upper extremity for 2 h/d, 3 d/wk, while restraining the nonaffected upper extremity with soft mitt for at least 5 h/d of their waking hours for 3 months. Shaping involved individualized task selection, graduated tasks difficulty and complexity, positive verbal feedback, and physical assisting with movements.[9] A behavioral contract detailed what activities would be done with the restraint on and when the restraint should be removed for potentially unsafe situations. The daily treatment diary assisted with ongoing evaluation of program adherence. The patients were strongly encouraged to continue using their weaker upper extremities during activities throughout the day and while at home.

The control group received conventional rehabilitation consisting of a 1-hour session of physiotherapy and 1-hour session of occupational therapy, 3 d/wk for 3 months. Therapy was based on neurodevelopmental techniques, focusing on normalizing tone and movement patterns and inhibition of abnormal tone and movement patterns. Restoration of stance, gait, dexterity, and stamina training exercises were primary targets. Upper limb exercises took approximately 40% of therapy time, mostly devoted to tone-inhibiting maneuvers and improving proximal muscle control.

Outcome Measures

The primary outcome measure was the MAS. The secondary outcome measures included real-world arm function (Motor Activity Log or MAL) and laboratory motor activity (Action Research Arm Test or ARAT). The assessment was conducted by an experienced investigator blinded to randomization.

1. The MAS is a 6-point ordinal scale commonly used in the measurement of spasticity severity and ranges from 0 (no spasticity) to 4 (affected part rigid in flexion or extension).[18] A supplementary level "1+" between scores "1" and "2" was allowed. For statistical purposes, MAS score "1" was considered as 1, MAS score "1+" as 2, and so on until 5 in this study. MAS has been shown to be reliable in the assessment of upper limb spasticity.[20]
2. The MAL is a valid and reliable scale of arm use and movement quality in real-world settings.[21,22] It includes a 6-point amount of use (AOU) scale and a 6-point quality of movement (QOM) scale to rate how much and how well patients are using their affected arms for common daily tasks.[21,22]
3. The ARAT is a functional assessment of upper extremity strength, dexterity, and coordination.[23] It includes 19 items focusing on grasping objects of different shapes and sizes, and gross movement in the vertical and horizontal planes. The performance of each task is rated on a 4-point scale, ranging from 0 (no movement possible) to 3 (movement performed normally). The maximum sum score is 57. The ARAT has high intrarater (r = .99) and test–retest (r = .98) reliability and validity.[24]

MAS and ARAT were evaluated before BtxA injection, at 4 weeks, 3 months, and 6 months postinjection. MAL was evaluated before injection, at 3 months, and 6 months postinjection. Two baseline ARAT assessments were performed 4 weeks apart, with the second assessment done just before BtxA injection. Baseline ARAT scores on 2 occasions were averaged for subsequent analyses.

Patients were asked to rate the level of global satisfaction resulting from the treatment on a 7-point categorical scale weighted from completely satisfied to completely dissatisfied at 3 months and 6 months postinjection. The safety of the treatment was assessed by recording the reported adverse events at each assessment visit.

Statistical Analysis

The sample size was calculated to give 90% power (α = .05, 2-tailed test) to detect a difference between the groups in posttreatment MAS scores of ≥1, assuming the standard deviation of the posttreatment scores was ≤0.9. A total of 15 patients in each group would tend to reach the power.

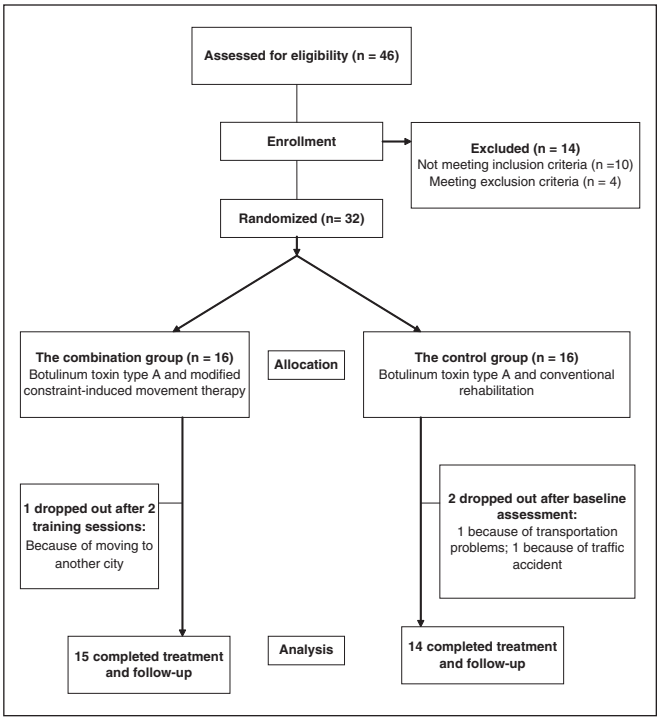

Figure 1. Flow diagram of participants through the trial.

Anticipating a dropout rate of 5% to 10%, we then increased the decided sample size to 16 patients in each group.

All statistical procedures were conducted with the Statistical Package for the Social Sciences (version 12.0; SPSS Inc, Chicago, IL). The data are presented as mean ± standard deviation, median value, or percentage in the text and figures. Baseline characteristics were compared using Mann–Whitney U tests, χ^2 tests or Fisher exact tests. Within-group changes from baseline in MAS, MAL, and ARAT were analyzed using the Wilcoxon signed rank tests at all follow-up visits. Between-group comparisons were performed using the Mann–Whitney U tests. P values <.05 were regarded as statistically significant.

Results

Of the 32 patients eligible for the study, 3 were excluded because they failed to complete the protocol. In all, 29 patients completed the study and were included in the analysis (Figure 1). The 2 groups were comparable at baseline with respect to their demographic data and clinical features (Table 1). Tables 2, 3, and 4 show the mean changes from baseline in the outcome scores at each following visit.

All patients demonstrated significant improvement in spasticity at 4 weeks and 3 months postinjection, without between-group differences (Tables 2 and 3). The median of MAS scores change of elbow, wrist, and finger flexors at 4-week and 3-month follow-up was −2 in all cases, except that the median of elbow MAS scores change was −1.5 in the control group at 3-month follow-up. At 6 months

Table 1. Demographic and Clinical Features of Study Patients[a]

Characteristic	Combination Group (n = 15)	Control Group (n = 14)
Age (years)	58.7 ± 9.9	61.5 ± 9.4
Female, n (%)	3 (20.0)	2 (21.4)
Diagnosis of infarction, n (%)	12 (80.0)	11 (78.6)
Paresis of right side, n (%)	11 (73.3)	9 (64.3)
Paresis of dominant side, n (%)	11 (73.3)	9 (64.3)
Body mass index (kg/m^2)	26.3 ± 4.1	27.2 ± 4.0
Years since first stroke	2.9 ± 1.5	2.9 ± 1.3
MAS		
Elbow	3.2 ± 0.4	3.2 ± 0.4
Wrist	2.8 ± 1.0	3.0 ± 0.8
Finger	3.2 ± 0.8	3.2 ± 0.4
MAL		
AOU scale	0.6 ± 0.6	0.6 ± 0.4
QOM scale	0.9 ± 0.6	0.8 ± 0.5
ARAT	32.1 ± 12.7	29.0 ± 14.1

Abbreviations: MAS, Modified Ashworth Scale (score range: 0-5); MAL, Motor Activity Log; AOU scale, amount of use scale (score range: 0-5); QOM scale, Quality of Movement Scale (score range: 0-5; higher scores representing better function); ARAT, Action Research Arm Test (score range: 0-57; higher scores representing better function).
[a] Values are mean ± standard deviation or percentage. None of the between-group differences were significant.

postinjection, there remained significant spasticity reduction from baseline in the elbow, wrist, and finger flexors in the combination group ($P = .004$, $P = .003$, and $P < .001$, respectively), with the median MAS scores change equal to −1 in all upper extremity flexors (Table 2). However, the benefit persisted only in the wrist flexors in the control group ($P = .014$), with the median MAS scores change equal to 0 (Table 3). Between-group comparisons showed a significant improvement in spasticity for the combination group in elbow, wrist, and finger flexors at 6 months postinjection ($P = .019$, $P = .019$, and $P < .001$, respectively; Table 2). It is noteworthy that most patients in the combination group demonstrated improvement in spasticity and that no patients worsened throughout the study period.

The combination group reported significantly larger improvements in the AOU scores than the control group at 3 months (1.1 ± 0.5 vs 0.1 ± 0.2; $P < .001$) and 6 months (1.2 ± 0.5 vs 0.1 ± 0.2; $P < .001$) postinjection (Table 4). On the QOM scale, the combination group also reported larger improvements than the control group at 3 months (0.9 ± 0.6 vs 0.3 ± 0.2; $P = .007$) and 6 months (1.0 ± 0.5 vs 0.1 ± 0.1; $P < .001$) postinjection. Both subscale scores of the MAL appeared to increase in the combination group at the 6-month follow-up, which suggested that patients did increase use of their affected limbs for daily activities.

Baseline ARAT scores on 2 occasions remained consistent in all patients, which suggested that they were exhibiting stable motor deficits. Both groups improved on the ARAT scores at 4-week postinjection without between-group differences (Table 4). The combination group displayed greater improvements on the ARAT scores than the control group, with significant between-group differences at 3 months (7.3 ± 5.0 vs 3.1 ± 2.6; $P = .012$) and 6 months (7.9 ± 5.2 vs 1.2 ± 1.7; $P < .001$) postinjection (Table 4).

Patient satisfaction is a fundamental goal in the treatment of stroke patients and it reflects the summation of all factors relating to successful clinical treatment. Results of patients' global satisfaction are shown in Table 5. Most patients were satisfied with the treatment. The combination group reported high subjective satisfaction at 3 months and 6 months postinjection (satisfaction rates = 93.3% and 86.7%, respectively). Although a decline in satisfaction was observed in both groups at 6 months postinjection, no patients reported dissatisfaction or aggravations of the upper limbs function throughout the study period.

The treatment was well tolerated by all patients. Local adverse events with mild transient pain at injection site were reported in 2 patients in each group. No upper extremity weakness or any incapacitating adverse events were reported.

To understand which factors may help to predict better MAS score change in the combination group, we compared the score changes by age, gender, education, side of stroke, stroke type (infarction or hemorrhage), disease duration, baseline AOU, QOM, and ARAT scores. A proportional test (P-test via binomial distribution) was used to test whether the proportions are different with different covariates. We found that none of these factors showed significant influence on MAS score change.

Discussion

To our knowledge, this is the first randomized controlled study investigating the treatment effects of combined BtxA and mCIMT for individuals with poststroke spasticity. The study demonstrated that combining BtxA and mCIMT was more superior to BtxA plus conventional rehabilitation in improving muscle tone and upper extremity motor function in chronic stroke patients with significant upper extremity spasticity. These effects persisted for at least 6 months. Patients reported considerable subjective satisfaction and no serious adverse events occurred.

These improvements of test scores in the combination group could be attributed to several factors. They could reflect improvement in strength and coordination in the affected upper extremity as a result of spasticity reduction and repetitive training, a change in learned nonuse behaviors, or use-dependent cortical changes after the combination of BtxA and mCIMT.

The primary outcome was evaluated with the MAS. A change of 1 point on the MAS is considered to be clinically significant.[2,25] We observed a clinically and statistically significant reduction in MAS scores at 4 weeks and 3 months postinjection in both groups. The results were consistent with

Table 2. Mean Change From Baseline in the Modified Ashworth Scale[a] (MAS) Scores in the Combination Group[b]

	MAS Change (Elbow)				MAS Change (Wrist)				MAS Change (Finger)			
Patient	Baseline	4 Weeks	3 Months	6 Months	Baseline	4 Weeks	3 Months	6 Months	Baseline	4 Weeks	3 Months	6 Months
A1	3	−2	−2	−2	3	−2	−2	−2	3	−2	−2	−1
A2	4	−1	−1	−1	4	−2	−2	−1	4	−3	−2	−1
A3	4	−1	−1	−1	4	−1	−1	−1	4	−2	−2	−1
A4	3	−2	−2	−2	3	−3	−3	−2	4	−3	−3	−1
A5	3	−2	−2	0	3	−2	−2	−2	4	−3	−3	−1
A6	3	−2	−2	−2	3	−2	−2	−2	2	−2	−1	−1
A7	3	−2	−2	0	3	−2	−2	−2	4	−3	−3	−2
A8	3	−2	−2	−2	1	−1	0	0	2	−1	−1	−1
A9	4	−3	−2	−1	3	−2	−1	−1	3	−3	−2	−1
A10	3	−2	−2	−2	1	−1	−1	0	3	−2	−2	−2
A11	3	−2	−2	−2	1	−1	−1	0	2	−2	−2	−1
A12	3	−2	−2	0	4	−3	−3	−1	4	−2	−2	−1
A13	3	−3	−2	0	3	−2	−2	−2	3	−2	−2	−2
A14	3	−2	−2	−2	3	−1	−1	−1	3	−3	−3	−2
A15	3	−2	−1	0	3	−1	−2	0	3	−2	−1	−1
	3.2 ± 0.4 (3)	−2.0 ± 0.5[c] (−2)	−1.8 ± 0.4[c] (−2)	−1.1 ± 0.9[d,e] (−1)	2.8 ± 1.0 (3)	−1.7 ± 0.7[d] (−2)	−1.7 ± 0.8[d] (−2)	−1.1 ± 0.8[d,e] (−1)	3.2 ± 0.8 (3)	−2.3 ± 0.6[c] (−2)	−2.1 ± 0.7[d] (−2)	−1.3 ± 0.5[c,f] (−1)

[a]MAS score range: 0 to 5.
[b]Values are mean ± standard deviation with medians in parentheses.
[c]Within group: $P < .001$ when compared with baseline values.
[d]Within group: $P < .05$ when compared with baseline values.
[e]Between groups: $P < .05$ when compared with the control group.
[f]Between groups: $P < .001$ when compared with the control group.

Table 3. Mean Change From Baseline in the Modified Ashworth Scale[a] (MAS) Scores in the Control Group[b]

	MAS Change (Elbow)				MAS Change (Wrist)				MAS Change (Finger)			
Patient	Baseline	4 Weeks	3 Months	6 Months	Baseline	4 Weeks	3 Months	6 Months	Baseline	4 Weeks	3 Months	6 Months
B1	3	−2	0	0	3	−3	−2	0	3	−2	−2	0
B2	3	−2	−2	−2	3	−3	−2	0	3	−3	−2	0
B3	4	−2	−3	0	3	−2	−2	0	4	−3	−3	0
B4	3	−1	−1	0	3	−1	−2	−1	3	−2	−2	0
B5	3	−2	−1	0	1	−1	0	0	3	−1	−1	−1
B6	4	−2	−2	−1	4	−1	−1	−1	4	−3	−1	0
B7	3	−2	−2	0	4	−1	−3	−1	3	−2	0	0
B8	4	−2	−1	0	4	−3	−3	0	4	−3	−1	0
B9	3	−2	0	0	3	−2	−1	0	3	−2	−1	0
B10	3	−2	−2	−1	3	−2	−2	−1	3	−3	−2	0
B11	3	−2	−2	0	2	−2	−1	−1	3	−2	−2	0
B12	3	−2	−1	−1	3	−2	−2	0	3	−2	−2	0
B13	3	−2	−2	0	3	−2	−2	−1	3	−3	−2	0
B14	3	−2	−1	0	3	−1	−1	0	3	−2	−2	0
	3.2 ± 0.4 (3)	−1.9 ± 0.3[c] (−2)	−1.4 ± 0.9[d] (−1.5)	−0.4 ± 0.6 (0)	3.0 ± 0.8 (3)	−1.9 ± 0.8[d] (−2)	−1.7 ± 0.8[d] (−2)	−0.4 ± 0.5[d] (0)	3.2 ± 0.4 (3)	−2.4 ± 0.6[d] (−2)	−1.6 ± 0.7[d] (−2)	−0.1 ± 0.3 (0)

[a]MAS score range: 0 to 5.
[b]Values are mean ± standard deviation with medians in parentheses.
[c]Within group: $P < .001$ when compared with baseline values.
[d]Within group: $P < .05$ when compared with baseline values.

Table 4. Mean Change From Baseline in the MAL and ARAT Scores[a]

Scale	Visit	Combination Group (n = 15)	Control Group (n = 14)
MAL, AOU scale	3 Months	1.1 ± 0.5 (1.1)[b,c]	0.1 ± 0.2 (0.1)[d]
	6 Months	1.2 ± 0.5 (1.3)[b,c]	0.1 ± 0.2 (0.0)
MAL, QOM scale	3 Months	0.9 ± 0.6 (0.9)[b,e]	0.3 ± 0.2 (0.3)[b]
	6 Months	1.0 ± 0.5 (1.0)[b,c]	0.1 ± 0.1 (0.1)[d]
ARAT	4 Weeks	3.9 ± 3.9 (3.0)[d]	2.1 ± 2.1 (1.5)[d]
	3 Months	7.3 ± 5.0 (6.0)[b,e]	3.1 ± 2.6 (2.0)[b]
	6 Months	7.9 ± 5.2 (6.0)[b,c]	1.2 ± 1.7 (1.0)[d]

Abbreviations: MAL, Motor Activity Log; AOU scale, Amount of Use scale (score range: 0-5); QOM scale, Quality of Movement scale (score range: 0-5); ARAT, Action Research Arm Test (score range: 0-57).
[a]Values are mean ± standard deviation with medians in parentheses.
[b]Within group: $P < .001$ when compared with baseline values.
[c]Between groups: $P < .001$ when compared with the control group.
[d]Within group: $P < 0.05$ when compared with baseline values.
[e]Between groups: $P < 0.05$ when compared with the control group.

Table 5. Patients' Global Satisfaction[a]

Group	Visit	Completely Satisfied	Satisfied	Somewhat Satisfied	No Change	Satisfaction Rate (%)
Combination group	3 Months	7	4	3	1	93.3
	6 Months	5	5	3	2	86.7
Control group	3 Months	3	5	3	3	78.6
	6 Months	2	2	5	5	64.3

[a]Numbers refer to number of patients who reported their level of global satisfaction with regard to the treatment when comparing the situation with that before the treatment. No patients reported dissatisfaction throughout the study period.

previous reports of BtxA on spasticity reduction.[2-4] Week 4 was chosen as the optimal time for the first outcome assessment time because of the clinical effect of BtxA peaked around this period.[26] Similarly, the timing of the subsequent assessments at 3 months was determined by the pharmacodynamic properties of BtxA because neurotransmission was restored in approximately 3 months by a process of neuronal sprouting.[27] Some authors recently showed that the contractile activity of the injected muscles might enhance the BtxA effect.[28,29] In this study, patients in the combination group continued using their injected upper extremities as much as possible, thus increased the overall contractile activity of the affected upper extremity and possibly produced greater reduction in spasticity and prolonged the BtxA effect duration to at least 6 months.

Before the intervention, all patients reported only occasional use of their affected upper extremities for daily activities, as reflected by the MAL, and substantial compromises in impairment and function, as measured by the MAS and ARAT, respectively. With the restraint on and the intensive training directed toward their affected upper extremities, patients in the combination group reported considerably larger improvements in the use and function of their affected upper extremities than those in the control group. This was evidenced by the MAL scores as well as through clinical observation. These findings were consistent with previous studies showing that MAL scores increased after a CIMT or mCIMT program.[13-15] It was appropriate to speculate that motivation and repeated task-specific practice through mCIMT might overcome a learned nonuse behavior. Without intensive task-specific training programs as adjunct therapy, improvements after BtxA injection might be short-lasting. This might account for the transient improvement in spasticity and the smaller improvement on ARAT in the control group. The limited improvement in the control group suggested that traditional neurorehabilitation have limited effectiveness in promoting motor recovery.

The motor changes in this study were not as sizable as those seen in previous mCIMT studies. One mCIMT study of patients (<14 days poststroke) receiving training for 10 weeks (3 d/wk) showed a mean improvement of +21.7 points on the ARAT.[16] Another study for chronic stroke patients (>1 year poststroke) showed improvement of +11.4 on the ARAT after participating in 10-week mCIMT program.[15] In our study, patients in the combination group showed a mean improvement of +7.9 points on the ARAT. It was important to note that our patients had relatively more severe motor impairment with significant upper extremity spasticity. We demonstrated that the treatment effects of mCIMT might be achieved during the period of chemodenervation provided by BtxA. The results were encouraging and this probably would expand the applicability of CIMT, as previous protocols often restrict

enrollment to stroke patients with established spasticity.[14-16] All patients entered this study at least 1 year after stroke, thus a contribution of spontaneous recovery was not likely. Data from our cases further refuted the notion that stroke patients could only exhibit gains up to 1 year poststroke.[30]

Although patients in this study showed improvement in MAS, MAL, and ARAT scores, it was not clear how increases in scores on any of these measures translate to real-world functional abilities. Whether such effects reflected cortical reorganization remains uncertain. Currently, it is unknown whether user-dependent cortical reorganization can occur in chronic patients with significant spasticity. Further research exploring central nervous system changes that accompany the observed motor gains is warranted.

After commencement of our present study, the report of Levy et al[31] appeared and the 2 sets of results support a similar conclusion. Levy et al reported in a preliminary study that BtxA plus exercise therapy showed potential to improve function for stroke patients with severe hand paresis and spasticity. Two of their patients who were unable to meet minimal motor criteria initially improved to meet the criteria and achieved further gains through CIMT. Our study with a larger sample size also supports the concept that improvement in hand function through BtxA and CIMT may be possible for stroke patients with upper extremity spasticity. The main difference of our study from that of Levy et al[31] was that we recruited patients who both met the minimal motor criteria and had significant spasticity, whereas Levy et al recruited poststroke spastic individuals unable to meet the minimal motor criteria. The modest successes of both studies suggest that a combination of BtxA and therapeutic approaches show promise in the treatment of poststroke hand paresis. However, the optimal combination awaits further investigation. Future research is needed to address the likely need for including rehabilitation with BtxA to improve function in patients with poststroke spasticity.

Several limitations existed in our study. First, we used a standard fixed-dosage BtxA regimen for all patients. An individualized approach based on the distribution of spasticity and the needs of the individual patient may optimize functional gains. Second, we did not administer objective measures of affected limb use such as activity monitors. Activities that could cause increases in upper limb spasticity during training need to be explored further. Third, because the sample size was relatively small, the specific characteristics of patients who would benefit most from this treatment were not found. Additional studies with larger sample size and longer follow-up period would be necessary to help to find predict factors for good response and determine the long-term effects of the combination therapy. The potential functional gains that may be acquired through earlier use of BtxA require further studies. The correlation between motor function changes and patients' satisfaction, the cost/benefit ratio, and quality-of-life perspective need careful consideration. Comparison studies with other potential therapeutic combinations, such as BtxA and electrical stimulation, are needed to determine the optimal treatment for patients with spasticity and limited motor ability.

Conclusion

On the basis of this prospective, randomized, controlled clinical trial, we concluded that combined BtxA and mCIMT produced significantly greater improvements in spasticity and upper extremity motor function than BtxA plus conventional rehabilitation in chronic stroke patients with upper extremity spasticity. The benefits could last for up to 6 months. The combined therapy resulted in high patients' satisfaction with no serious adverse events. The results provide support for introducing this promising combination into clinical practice.

Acknowledgments

We wish to express our sincere gratitude to all the investigators, therapists, and patients who participated in the trial. The authors also wish to thank Kam-Fai Wong and Luo-Ping Ger, MPH, for their skillful assistance with statistical analysis.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The study was supported by a grant of VGHKS94-087 (an academic research fund for Kaohsiung Veterans General Hospital, Taiwan).

References

1. Wade DT, Collen FM, Robb GF, Warlow CP. Physiotherapy intervention late after stroke and morbidity. *BMJ.* 1992;304: 609-613.
2. Simpson DM, Alexander DN, O'Brien CF, et al. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology.* 1996;46:1306-1310.
3. Bakheit AM, Thilmann AF, Ward AB, et al. A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb muscle spasticity after stroke. *Stroke.* 2000;31:2402-2406.
4. Bhakta BB, Cozens JA, Chamberlain MA, Bamford JM, et al. Impact of botulinum toxin on disability and carer burden due to arm spasticity after stroke: a randomized double blind placebo controlled trial. *J Neurol Neurosurg Psychiatry.* 2000;69: 217-221.
5. Brashear A, Gordon MF, Elovic E, et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med.* 2002;347:395-400.
6. Sahrmann SA, Norton BJ. The relationship of voluntary movement to spasticity in the upper motor neuron syndrome. *Trans Am Neurol Assoc.* 1977;102:108-111.

7. Knutsson E, Martensson A. Dynamic motor capacity in spastic paresis and its relation to prime mover dysfunction, spastic reflexes and agonist co-activation. *Scand J Rehabil Med.* 1980;12:93-106.
8. Page SJ, Elovic E, Levine P, Sisto SA. Modified constraint-induced therapy and botulinum toxin A: a promising combination. *Am J Phys Med Rehabil.* 2003;82:76-80.
9. Taub E, Uswatte G, Pidikiti R. Constraint-induced movement therapy: a new family of techniques with broad application to physical rehabilitation—a clinical review. *J Rehabil Res Dev.* 1999;36:237-251.
10. van der Lee JH, Wagenaar RC, Lankhorst GJ, Wogelaar TW, Devillé WL, Bouter LM. Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial. *Stroke.* 1999;30:2369-2375.
11. Wolf SL, Winstein CJ, Miller JP, et al; EXCITE investigators. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA.* 2006;296:2095-2104.
12. Lin KC, Wu CY, Liu JS, Chen YT, Hsu CJ. Constraint-induced therapy versus dose-matched control intervention to improve motor ability, basic/extended daily functions, and quality of life in stroke. *Neurorehabil Neural Repair.* 2009;23:160-165.
13. Miltner WH, Bauder H, Sommer M, Dettmers C, Taub E. Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke: a replication. *Stroke.* 1999;30:586-592.
14. Page SJ, Sisto SA, Levine P, Johnston MV, Hughes M. Modified constraint induced therapy: a randomized, feasibility and efficacy study. *J Rehabil Res Dev.* 2001;38:583-590.
15. Page SJ, Sisto S, Levine P, McGrath RE. Efficacy of modified constraint induced therapy in chronic stroke: a single blinded randomized controlled trial. *Arch Phys Med Rehabil.* 2004;85:14-18.
16. Page SJ, Levine P, Leonard AC. Modified constraint-induced therapy in acute stroke: a randomized controlled pilot study. *Neurorehabil Neural Repair.* 2005;19:27-32.
17. Sun SF, Hsu CW, Hwang CW, Hsu PT, Wang JL, Yang CL. Application of combined botulinum toxin type A and modified constraint-induced movement therapy for an individual with chronic upper-extremity spasticity after stroke. *Phys Ther.* 2006;86:1387-1397.
18. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther.* 1987;67:206-207.
19. Bleecker ML, Bolla-Wilson K, Kawas C, Agnew J. Age-specific norms for the Mini-Mental State Exam. *Neurology.* 1988;38:1565-1568.
20. Gregson JM, Leathley M, Moore AP, Sharma AK, Smith TL, Watkins CL. Reliability of the tone assessment scale and the modified Ashworth scale as clinical tools for assessing post-stroke spasticity. *Arch Phys Med Rehabil.* 1999;80:1013-1016.
21. Uswatte G, Taub E, Morris D, Vignolo M, McCulloch K. Reliability and validity of the upper-extremity Motor Activity Log-14 for measuring real-world arm use. *Stroke.* 2005;36:2493-2496.
22. van der Lee J, Beckerman H, Knol D, de Vet HC, Bouter LM. Clinimetric properties of the motor activity log for the assessment of arm use in hemiparetic patients. *Stroke.* 2004;35:1-5.
23. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *Int J Rehabil Res.* 1981;4:483-492.
24. van der Lee JH, De Groot V, Beckerman H, Wagenaar RC, Lankhorst GJ, Bouter LM. The intra- and interrater reliability of the Action Research Arm test: a practical test of upper extremity function in patients with stroke. *Arch Phys Med Rehabil.* 2001;82:14-19.
25. Albright AL, Barron WB, Fasick MP, Polinko P, Janosky J. Continuous intrathecal baclofen infusion for spasticity of cerebral origin. *JAMA.* 1993;270:2475-2477.
26. Jankovic J, Schwartz K. Botulinum toxin injections for cervical dystonia. *Neurology.* 1990;40:277-280.
27. de Paiva A, Meunier FA, Molgo J. Functional repair of motor endplates after botulinum toxin-A poisoning: bi-phasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc Natl Acad Sci U S A*. 1999;96:3200-3205.
28. Hesse S, Jahnke MT, Luecke D, Mauritz KH. Short-term electrical stimulation enhances the effectiveness of Botulinum toxin in the treatment of lower limb spasticity in hemiparetic patients. *Neurosci Lett.* 1995;201:37-40.
29. Eleopra R, Tugnoli V, De Grandis D. The variability in the clinical effect induced by botulinum toxin type A: the role of muscle activity in humans. *Mov Disord.* 1997;12:89-94.
30. Jørgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Støier M, Olsen TS. Outcome and time course of recovery in stroke. Part II: time course of recovery. The Copenhagen Stroke Study. *Arch Phys Med Rehabil.* 1995;76:406-412.
31. Levy CE, Giuffrida C, Richards L, Wu S, Davis S, Nadeau SE. Botulinum toxin A, evidence-based exercise therapy, and constraint-induced movement therapy for upper-limb hemiparesis attributable to stroke: a preliminary study. *Am J Phys Med Rehabil.* 2007;86:696-706.