Constraint-Induced Movement Therapy During Early Stroke Rehabilitation

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Background. Limited data are available about the effectiveness of early rehabilitation after stroke. *Objective.* This is the 1st randomized controlled trial of constraint-induced movement therapy (CIMT) in subacute stroke to investigate neurophysiologic mechanisms and long-term outcome. *Methods.* Within 2 weeks after stroke, 23 patients with upper extremity (UE) weakness were randomized to 2 weeks of CIMT or traditional therapy at an equal frequency of up to 3 h/day. Motor function of the affected UE was blindly assessed before treatment, after treatment, and 3 months after stroke. Transcranial magnetic stimulation (TMS) measured the cortical area evoking movement of the affected hand. *Results.* Long-term improvement in motor function of the affected UE did not differ significantly between patients who received CIMT versus intensive traditional therapy. All outcome comparisons showed trends favoring CIMT over intensive traditional therapy, but none was statistically significant except for improvements in the Fugl-Meyer (FM) UE motor scale immediately following treatment and in reported quality of hand function at 3 months. Improvement in UE motor function on the FM was associated with a greater number of sites on the affected cerebral hemisphere where responses of the affected hand were evoked by TMS. *Conclusions.* Future trials of CIMT during early stroke rehabilitation need greater statistical power, more inclusive eligibility criteria, and improved experimental control over treatment intensity. The relationship between changes in motor function and in evoked motor responses suggests that motor recovery during the 1st 3 months after stroke is associated with increased motor excitability of the affected cerebral hemisphere.

Key Words: *Stroke—Cerebrovascular disorders—Hemiplegia—Randomized controlled trial—Rehabilitation—Transcranial magnetic stimulation.*

Constraint-induced movement therapy (CIMT) is a rehabilitation technique for hemiparesis developed in the laboratory of one of the authors (ET) that consists of restraining the unaffected upper extremity (UE) while intensively training the affected arm and hand to improve performance on functional motor tasks.[1,2] Although the effectiveness of CIMT in chronic stroke is well established,[3-6] support for CIMT early after stroke is limited to a single clinical trial involving hospitalized patients[7] in which outcome was measured immediately after completion of therapy without including a follow-up assessment. Apart from preliminary reports from the current study,[8,9] no data are available about the long-term maintenance of therapeutic gains or about the neurophysiologic mechanisms that mediate the effects of early therapy. This article reports a clinical trial of CIMT during early stroke rehabilitation that is the 1st controlled study to evaluate whether improved motor function is maintained after treatment and to investigate how neurophysiologic changes resulting from therapy are related to therapeutic gains.

The major aim of this single-blind randomized clinical trial was to evaluate whether providing 2 weeks of CIMT initiated within 2 weeks of unilateral stroke was feasible and induced lasting beneficial changes in motor function of the affected upper limb. The study used a parallel-groups design comparing a group of patients who received CIMT with a control group receiving therapy consisting of traditional techniques. Frequency and duration of therapy were equated between the treatment groups to avoid confounding type of therapy with the intensity of intervention. Motor function was measured by behavioral motor performance tests and by self-report. A follow-up assessment at 3 to 4 months after stroke evaluated whether therapeutic gains had

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Boake C, Noser EA, Ro T, Baraniuk S, Gaber M, Johnson R, Salmeron ET, Tran TM, Lai JM, Taub E, Moye LA, Grotta JC, Levin HS. Constraint-induced movement therapy during early stroke rehabilitation. *Neurorehabil Neural Repair* 2007;21:14–24.

DOI: 10.1177/1545968306291858

been maintained. A secondary aim was to investigate neurophysiologic mechanisms that mediated effects of therapy, using transcranial magnetic stimulation (TMS) to map the cortical hand area of the stroke hemisphere. TMS was coadministered on the same occasions as behavioral testing in order to explore correlations between motor recovery and neurophysiologic changes.

METHODS

Patients

Adult stroke patients were recruited from March 2001 to October 2004 from admissions to the in-patient Stroke Service of Memorial Hermann Hospital, a teaching hospital in Houston, TX, which is affiliated with the University of Texas-Houston Medical School. Criteria for enrollment were ischemic or hemorrhagic stroke within 14 days of entering the trial; stroke lesion visualized on computed tomography or magnetic resonance imaging scan of the brain performed before enrollment; score of 1 to 3 on item 5 (arm motor) of the National Institutes of Health (NIH) Stroke Scale (NIHSS);[10] at least 10 deg of active movement in the thumb and 2 or more fingers of the affected hand; total NIHSS score ≤14 if right- and ≤19 if left-sided stroke; ability to provide informed consent; no previous stroke that would interfere with interpretation of the results; no neglect or speech comprehension impairment that would prevent participation in the study assessments and treatment; no pacemaker or other metallic implant; no UE orthopedic limitation that would affect the results; and readiness to participate in standard rehabilitation at the time of enrollment. The NIHSS arm motor score criterion excluded patients with no arm movement at all, or no detectable shoulder weakness. The requirement of active movement in the thumb and fingers ensured that motor function would have been sufficient to perform the CIMT training tasks.

Outcome Measures

Fugl-Meyer Assessment of Motor Recovery.[11] The Fugl-Meyer Assessment of Motor Recovery (FM), a motor performance test consisting of 33 tasks performed by the affected UE, evaluates the ability to make movements outside of a synergistic pattern. Performance on each task is rated 0, 1, or 2, with higher ratings representing better performance. The FM measure used in this study was the sum of the 33 ratings (possible range 0 to 66).

Grooved Pegboard Test.[12] The Grooved Pegboard Test (GPT), a test of manual dexterity, evaluates the speed with which the patient grasps and inserts 25 pegs (3 cm length, 5 mm diameter) into a grid of vertical holes in a horizontal 10 cm square surface. The test was discontinued at 150 s if the patient was unable to insert any pegs. The GPT measure for each hand was the number of pegs placed per second. The worst possible value of 0 was earned by patients who did not place any pegs. Performance by the unaffected hand was used to measure adverse effects of wearing the restraint.

Motor Activity Log.[1,13] The Motor Activity Log (MAL), a rating scale, evaluates how the affected hand is used to perform 30 daily living activities (e.g., feeding, turning a door handle). For each activity, the patient rates how much the affected hand is used (amount of use) and how well the activity is performed (quality of movement). Ratings are on a scale from 0 to 5, with higher scores representing better function. The MAL measures were the average ratings for amount of use and for quality of use. The standard MAL was modified for this study by omitting 8 activities that could not be performed during in-patient hospitalization (e.g., turning an ignition key). The MAL was administered only at baseline and at the 2 outcome assessments, and not during the treatment period.

Transcranial magnetic stimulation. The hand motor area of each cerebral hemisphere was mapped using TMS according to procedures previously validated[14,15] and detailed in our preliminary article.[9] TMS was delivered by a Cadwell Laboratories MES-10 polyphasic stimulator (Kennewick, WA). Electromyographic (EMG) activity of the abductor pollicis brevis (APB) of the resting hand contralateral to stimulation was recorded using silver-silver chloride surface electrodes attached to a Grass-Astromed (model IP511, West Warwick, RI) amplifier and digitized by a data acquisition card (model CYDAS 8, CyberResearch, Inc., Branford, CT). The EMG signal was amplified and filtered for frequencies between 30 Hz and 1000 Hz and was sampled at 1 kHz. During each TMS session, both hemispheres were mapped and the order of the hemispheres was counterbalanced across patients and sessions. The hand area and TMS motor threshold for each hemisphere were established at the beginning of the session. The motor threshold was determined at each session, and TMS intensity at each session was determined relative to the current threshold. For each hemisphere, TMS intensity was set at 10% above the motor threshold, defined as the lowest intensity that induced activation of the contralateral hand on at least 3 of 5 trials. The threshold definition of 3 out of 5 trials was justified by the need to minimize fatigue caused by the long sitting time required of the subacute stroke patients during extensive TMS and motor testing sessions. Once the cortical hand area had been localized, TMS was applied systematically to locations marked directly on the scalp at steps of 1 cm from the initial hand localization site. Activation of a site

was defined as a TMS-evoked motor response detected by EMG or visually observed movement by 2 observers on any area of the hand on at least 3 of 5 trials. Visual observation was used as the sole criterion when EMG was unavailable (e.g., technical problems). Both EMG and visual inspection were recorded during the majority of TMS sessions, and both were used as activation criteria. Thus, during TMS mapping, a given scalp position was classified as an activation site if either criterion had been met on 3 of 5 trials. Correspondence between EMG and visual inspection was evaluated in our preliminary study[9] and was found to be high. Stimulation was continued until demarcating an area of active sites surrounded by a border of sites at which the evoked motor responses did not meet either the EMG or visual observation criteria (cf. reference 9). In some cases, when TMS of the border regions activated some hand movements, but not enough to meet the criterion of activation on at least 3 out of 5 trials, locations outside this border were also tested to ensure that no more activation sites could be detected. The dependent measures for each hemisphere were the number of TMS activation sites and the motor threshold. If fewer than 3 motor responses were evoked at any position on the affected hemisphere, then the number of stroke-hemisphere TMS activation sites was defined as zero and the motor threshold was defined as greater than 100%.

Treatment

Constraint-induced movement therapy. Therapy sessions consisted of performing tasks only with the affected UE. Task movements included reaching, grasping, lifting, and placing. Tasks were individually selected according to motor ability, to ensure successful experience and prevent frustration leading to learned nonuse.[1,16] Task difficulty was progressively increased using behavioral techniques of shaping and successive approximation.[17] In addition to individual therapy sessions, patients were asked to wear a mitten restraint (Sammons Preston #6727 "Padded Safety Mitt," Sammons Preston, Inc., Bolingbrook, IL) on the unaffected hand during 90% of waking hours, excluding activities when risk of injury might increase. The mitten allowed the unaffected UE to assist in transfers and ambulation, but it prevented use of the unaffected fingers to manipulate objects and necessitated use of the affected hand to perform daily activities.

Intensive traditional therapy. Therapy sessions consisted of performing daily living tasks with either hand and therapeutic activities with the affected UE that were intended to improve strength, muscle tone, and range of motion. This treatment condition differed from the standard therapy regimen provided to non-study-patients in that the number of hours of therapy per day and the number of therapy days were increased to approximate the frequency and duration of CIMT. No restraint was used, and patients were free to use either hand for daily activities.

Procedure

The study was approved by the Committee for the Protection of Human Subjects at the University of Texas-Houston Medical School. Consecutive patients admitted to the stroke unit of Memorial Hermann Hospital were screened for eligibility. After giving informed consent, eligible patients underwent baseline testing and were randomly allocated to either CIMT or traditional therapy. Randomization was stratified for age (≤60 years or >60 years) and NIHSS arm motor score (1 or 2–3). The NIHSS arm motor score was selected for stratification because of its prognostic value, because the score levels are appropriate to classify patients for our study, and because the score distribution in our stroke admissions was already known. Therapy began on the day of baseline testing or the following day, at a median of 11 days after stroke (range 5 to 19 days). All patients received either CIMT or traditional UE therapy at an equal frequency and duration of up to 3 h per day, for 14 to 15 days at a frequency of 6 days per week excluding Sundays. This procedure controlled the number of hours of therapy time, but not energy expended during therapy. Intervention was provided by licensed therapists and therapy assistants, including an occupational therapist (MG) and a physical therapist who had undergone training in Dr. Taub's laboratory at the University of Alabama at Birmingham and who provided or supervised the UE therapy for all patients. Most patients began the study therapy on the in-patient rehabilitation unit, were discharged from the hospital during the therapy period, and completed the remaining therapy sessions in the out patient rehabilitation clinic. Motor tests and TMS mapping were repeated 2 times after treatment. The 1st occasion was a posttreatment evaluation immediately after completing therapy, and the 2nd was a follow-up evaluation 3 to 4 months after stroke. Motor testing and TMS mapping of a given patient were generally performed on the same day, but the order of these procedures was not controlled. Outcome evaluations were performed by personnel from outside of Memorial Hermann Hospital who were blind to treatment assignment.

Analyses

This was a randomized clinical study with 2 treatment groups (CIMT and intensive traditional therapy)

Table 1. Demographic and Clinical Features of Patients Receiving Study Therapy

	CIMT	Traditional Therapy
N	10	13
Age, *M* (*SD*)	63.1 (14.3)	58.9 (14.0)
Sex, *n*		
Female	3	5
Male	7	8
Affected side, *n*		
Left	6	6
Right	4	7
NIHSS total score, *M* (*SD*)	4.9 (1.8)	5.3 (3.4)
NIHSS arm motor score, *M* (*SD*)	1.6 (0.84)	1.46 (0.77)
Type of stroke, *n*		
Infarct	9	9
Hemorrhage	1	4
Stroke location, *n*		
Cortical	2	3
Subcortical	5	8
Brainstem	3	2

CIMT = constraint-induced movement therapy; NIHSS = National Institutes of Health Stroke Scale.

in a relatively small number of individuals. Baseline measures of demographics and comorbidity were assessed using Fisher's exact test for dichotomous variables and student's *t* test for continuous variables.

The prospectively declared endpoint for this study was the impact of the intervention on the change of the FM score over time, from the baseline to the follow-up assessment. Thus, the change in this measure in the CIMT group was compared to the change in this measure in the control group. The estimates necessary to complete the sample size calculation for this trial were determined from analyses performed on the 1st 8 patients of this study.[9] From this evaluation, the observed FM effect size (i.e., change in active group minus change in the control group) was 14.5, with a standard deviation of 10.76 in the CIMT group and 11.36 in the control group. A standard sample size computation determined that a total of 24 patients (12 in each of the groups) were required to have 90% power to detect the full effect size for a 2-sided type I error of 0.05.

We used descriptive statistics (means, medians, and standard deviations) to summarize the data. Any patient with missing or incomplete FM data at baseline or follow-up was excluded from the principal analysis of the primary endpoint. A 2-sided test of significance was carried out for the primary outcome, with an alpha level of 0.045, consistent with an alpha spending function that permitted the interim analysis. The evaluation of the impact of the intervention on 2 other functional measures (GPT and MAL) was prospectively declared. However, they did not have their type I error rates corrected for multiple comparisons and are secondary endpoints, with *P* value assessment at the nominal 0.05 level. The remaining analyses were exploratory. We used Pearson correlations to examine the association between UE motor performance and number of TMS active sites in the affected cerebral hemisphere. We used the Wilcoxon 2-sample test to compare stroke-hemisphere motor thresholds between the 2 treatment groups at each of the 3 TMS assessments. The nonparametric test was used to include patients who had no stroke-hemisphere TMS activation sites.

RESULTS

Feasibility and Safety

Table 1 presents the demographic and clinical features of the patients who met entry criteria and were randomized. The treatment groups did not differ significantly in baseline characteristics, including side of stroke. All randomized patients underwent the planned series of therapy sessions. Time from stroke to the follow-up evaluation averaged 104.2 days in the CIMT group (range 91–137 days) and 108.4 days in the control group (range 92–143 days). No significant adverse events occurred during the therapy period. No seizures were induced by TMS. No patient had a recurrent stroke during participation in the study.

At baseline, the FM was not completed by 1 control patient. One CIMT patient was not administered the MAL at baseline and posttreatment owing to aphasia. At follow-up, 1 control patient was not administered the FM and GPT because of UE injury unrelated to the study, and 1 control patient had missing GPT data. Two control patients did not complete any measures at follow-up because of refusal to participate and change of residence to a different city. Three patients (2 control, 1 CIMT) had incomplete FM administrations at baseline or follow-up because of omission of up to 3 items due to examiner error. Because of these difficulties obtaining complete data, FM results are reported separately for the 16 patients (9 CIMT, 7 control) who had complete FM data at both the baseline and follow-up assessments (complete cohort). Figure 1 shows for the complete cohort the flow of patients through the study and collection of the FM data. FM results are also reported for the 22 patients (10 CIMT, 12 control) including those who had incomplete FM data caused by omission of up to 3 items, or who had missing FM data at follow-up (total cohort). For the total cohort, FM scores for the 3 patients with omitted items were obtained by assigning a rating of zero (worst possible score) for those items. For the 3 patients with no follow-up FM

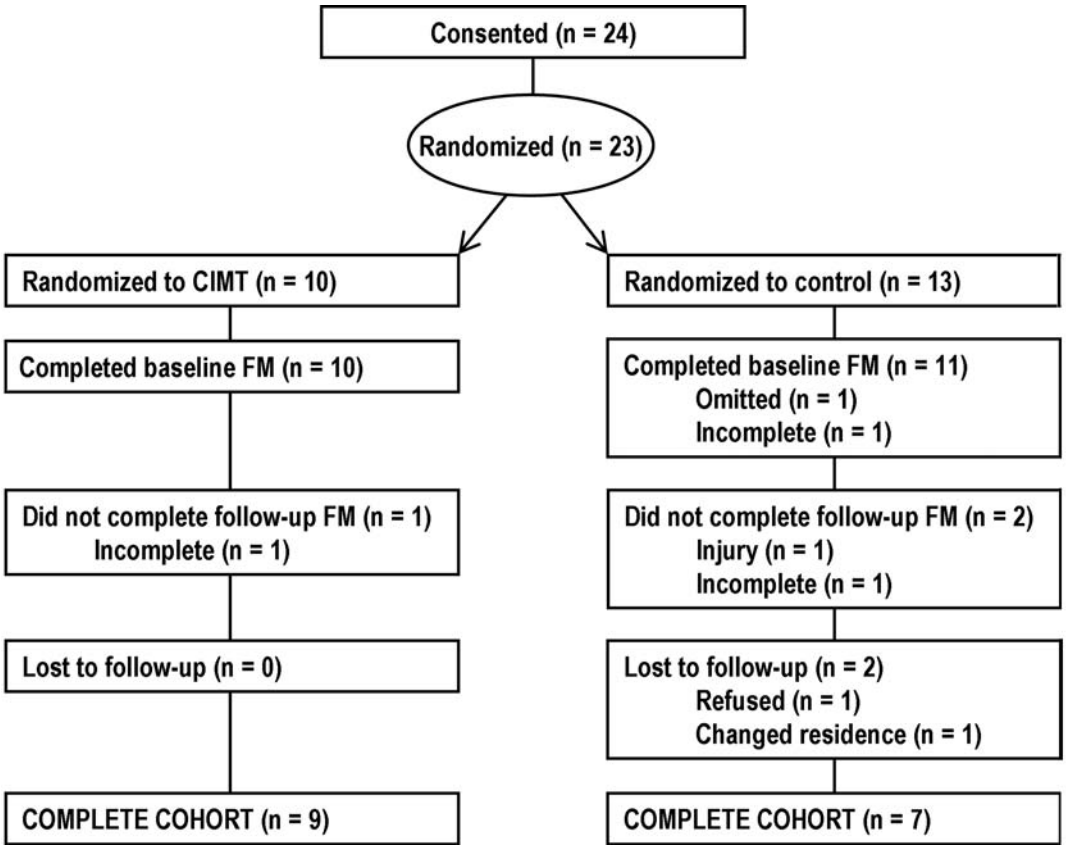

Figure 1. Flowchart of the flow of patients through the study and collection of the Fugl-Meyer (FM) upper-extremity motor scale. The complete cohort includes only patients with complete FM data at both the baseline and follow-up assessments. CIMT = constraint-induced movement therapy.

data, FM results at the posttreatment evaluation were carried forward. These conventions were determined prospectively, before unblinding of results.

Motor Skills

Tables 2 and 3 show the results for both treatment groups on measures of motor performance, self-report, and TMS assessed at baseline, immediately after treatment, and at follow-up 3 to 4 months after stroke. Improvement was seen in both treatment groups on all measures of motor function in the affected UE.

All of the comparisons of motor performance between the CIMT and intensive traditional therapy group were in the predicted direction (i.e., greater improvement in affected UE function in the CIMT group), but the primary outcome was not statistically significant. Change in FM from baseline to 3 months, which was the prospectively declared primary endpoint, showed improvement in both treatment groups, although the apparent advantage of the CIMT group was not statistically significant (complete cohort: $t = 1.43$, $df = 14$, $P = 0.137$, 95% confidence interval [CI] of mean difference = –3.81, 24.95; total cohort: $t = 1.47$, $df = 20$, $P = 0.157$, 95% CI of mean difference = –3.28, 18.98). The CI of the difference between treatment group means is coded so that positive values indicate an advantage for the group receiving CIMT.

Results for the secondary endpoints were as follows. For the FM, improvement from baseline to posttreatment was significantly greater in the CIMT group for the 16 patients with complete data ($t = 2.15$, $df = 14$, $P = 0.0497$, 95% CI of mean difference = 0.011, 16.88) but not in the total cohort of 22 patients ($t = 1.21$, $df = 20$, $P = 0.237$, 95% CI of mean difference = –3.28, 12.51). Results for the GPT and MAL were analyzed for patients with complete data at baseline and follow-up. For the GPT, performance by the affected hand improved from baseline to follow-up in all patients, without the CIMT and intensive traditional therapy groups differing significantly ($t = 1.49$, $df = 17$, $P = 0.153$, 95% CI of mean difference = –0.02, 0.12). For the MAL, improvement in the CIMT group from baseline to follow-up was significantly better for quality ($t = 2.30$, $df = 18$, $P = 0.033$, 95% CI of mean difference = 0.11, 2.32) but not for amount ($t = 1.86$, $df = 18$, $P = 0.080$, 95% CI of

Table 2. Fugl-Meyer Assessment Upper-Extremity Motor Scale: Complete and Total Cohort

	Baseline	Posttreatment	Follow-up	Difference Follow-up-Baseline
Complete cohort, *M* (*SD*) *n* = 16				
CIMT	29.44 (12.11)	47.89 (6.71)	53.44 (8.63)	24.00 (14.60)
Traditional therapy	36.71 (14.22)	46.71 (14.88)	50.14 (10.88)	13.43 (11.34)
Total cohort, *M* (*SD*) *n* = 22				
CIMT	30.8 (12.20)	49.0 (7.24)	54.4 (8.68)	23.6 (13.82)
Traditional therapy	29.5 (18.35)	43.6 (14.02)	45.5 (14.4)	15.7 (11.2)

CIMT = constraint-induced movement therapy.

Table 3. Grooved Pegboard Test and Motor Activity Log

	Baseline	Posttreatment	Follow-up
Grooved Pegboard affected side, *M* (*SD*)			
CIMT	0.01 (0.027)	0.078 (0.063)	0.163 (0.062)
Traditional therapy	0.0046 (0.015)	0.041 (0.075)	0.108 (0.101)
Grooved Pegboard unaffected side, *M* (*SD*)			
CIMT	0.179 (0.051)	0.256 (0.107)	0.243 (0.059)
Traditional therapy	0.183 (0.073)	0.229 (0.078)	0.268 (0.097)
Motor Activity Log–Amount of Use, *M* (*SD*)			
CIMT	0.479 (0.426)	2.21 (1.41)	3.10 (1.40)
Traditional therapy	0.690 (0.770)	1.94 (1.49)	2.23 (1.39)
Motor Activity Log–Quality of Use, *M* (*SD*)			
CIMT	0.474 (0.314)	2.07 (1.26)	3.27 (1.28)
Traditional therapy	0.764 (0.805)	1.82 (1.26)	2.29 (1.38)

CIMT = constraint-induced movement therapy.

mean difference = –0.13, 2.16). GPT performance by the unaffected hand showed no worsening over time and no difference between groups.

In view of the discrepancy in motor results from the preliminary study, which had revealed a large advantage of CIMT relative to the control condition,[8,9] we carried out exploratory analyses of differences in baseline characteristics between patients in the preliminary study and those treated afterward. These analyses revealed a difference in UE motor impairment as measured by the NIHSS arm motor score at baseline, with the 8 patients in the preliminary study exhibiting greater shoulder weakness (mean = 2.25, *SD* = 0.89) relative to the final 15 patients (mean = 1.20, *SD* = 0.56) ($t = 3.49$, $df = 21$, $P = 0.002$, 95% CI of mean difference = 0.42, 1.68). We attempted to identify patient characteristics associated with greater response to CIMT relative to the control condition, but these subgroup analyses were not viable because of small sample sizes.

Transcranial Magnetic Stimulation

Tables 4 and 5 show the TMS results at the same 3 occasions. TMS was not completed in the 1st 3 enrolled patients (2 control, 1 CIMT) at posttreatment and in the 2 patients (both controls) who were lost to follow-up. As seen in Tables 4 and 5, at the baseline evaluation, most patients in both treatment groups had no TMS activation sites in the affected hemisphere, and therefore the median motor threshold could not be estimated. Over the study period, there was a dramatic increase in the proportion of patients in whom movements of the affected hand were evoked by TMS, as is consistent with the expected course of recovery after stroke. However, there was no statistically significant difference in motor threshold between the 2 treatment groups at baseline (Wilcoxon statistic = 134.5, $Z = 1.02$, $P = 0.318$), the evaluation immediately after treatment (Wilcoxon statistic = 96.0, $Z = 0.08$, $P = 0.940$), or the follow-up evaluation at 3 months poststroke (Wilcoxon statistic = 110.0, $Z = 0.0$, $P = 1.0$).

Data for the number of active TMS sites in the stroke and nonstroke hemisphere are summarized in Table 4, and individual patient data are presented in Table 5. In the stroke hemisphere, no specific effect of CIMT was apparent in the number of TMS activation sites detected at the immediate posttreatment evaluation. The mean number of stroke-hemisphere TMS activation sites at this evaluation did not differ between patients who had been evaluated on the final day of treatment versus those tested later (means 3.55 and 4.67,

Table 4. Transcranial Magnetic Stimulation Motor Threshold, Number of Patients Without Motor-Evoked Potential, and Number of Active Transcranial Magnetic Stimulation Sites

	Baseline	Posttreatment	Follow-up
Patients without stroke-hemisphere MEP, *n* without MEP/*n* tested			
CIMT	8/10	2/9	1/10
Traditional therapy	7/13	2/11	1/11
Motor threshold (%MSO) in stroke hemisphere, Mdn			
CIMT	> 100	83.0	75.0
Traditional therapy	> 100	83.0	67.0
Active TMS sites in stroke hemisphere, *M* (*SD*)			
CIMT	1.00 (2.16)	3.00 (2.12)	6.10 (3.28)
Traditional therapy	1.53 (2.22)	4.09 (3.39)	4.54 (2.84)
Active TMS sites in nonstroke hemisphere, *M* (*SD*)			
CIMT	7.00 (4.66)	6.56 (2.83)	5.70 (4.14)
Traditional therapy	4.54 (2.07)	4.55 (1.81)	5.36 (1.86)

MEP = motor evoked potential; CIMT = constraint-induced movement therapy; MSO = maximum stimulator output; Mdn = median; TMS = transcranial magnetic stimulation.

Table 5. Number of Active Transcranial Magnetic Stimulation Sites Detected in Individual Patients

	Stroke Hemisphere			Nonstroke Hemisphere		
Group/Patient #	Baseline	Posttreatment	Follow-up	Baseline	Posttreatment	Follow-up
CIMT						
3	0	NT	8	7	NT	2
4	0	7	10	9	5	14
7	0	3	11	6	10	5
8	0	0	7	19	12	12
11	0	3	4	5	5	1
13	0	3	5	6	8	6
14	4	4	6	4	6	4
18	0	0	0	3	4	4
21	6	4	7	3	4	5
22	0	3	3	8	5	4
Traditional therapy						
1	0	NT	1	1	NT	2
2	1	NT	9	3	NT	6
5	0	0	0	4	4	3
6	0	0	2	6	4	8
9	0	4	NT	5	2	NT
10	6	11	4	6	8	5
12	2	8	8	5	5	6
15	0	5	7	5	5	5
16	0	2	4	6	6	4
19	6	7	NT	1	5	NT
20	2	4	6	6	2	6
23	3	6	4	3	6	8
24	0	7	5	8	3	6

CIMT = constraint-induced movement therapy; NT = not tested.

respectively; $t = 0.83$, $df = 18$, $P = 0.418$, 95% CI of mean difference = –3.96, 1.72). The number of active TMS stroke-hemisphere sites increased in both treatment groups from baseline to follow-up, at which time it approximated the number of active sites in the nonstroke hemisphere. The increase in the number of stroke-hemisphere activation sites from baseline to follow-up was greater in the CIMT patients than in the intensive traditional therapy patients, as in our preliminary results,[9] but the difference was not statistically significant ($t = 1.20$, $df = 19$, $P = 0.241$, 95% CI of mean difference = –1.33, 4.99). In the nonstroke hemisphere,

Table 6. Correlation of Motor Performance With Number of Active Transcranial Magnetic Stimulation Sites in the Stroke Hemisphere

Motor Test	Baseline	Follow-up	Difference Follow-up-Baseline
Fugl-Meyer upper-extremity motor scale, *r*			
All patients	0.45*	0.47*	0.50*
CIMT	0.69*	0.59	0.69*
Traditional therapy	0.35	0.36	0.14
Grooved Pegboard Test, *r*			
All patients	0.15	0.35	0.32
CIMT	0.47	0.70*	0.70*
Traditional therapy	–0.20	0.02	–0.07

CIMT = constraint-induced movement therapy.
*$P < 0.05$, 2-tailed.

the number of activation sites decreased slightly from baseline to follow-up in the CIMT patients but the observed change did not differ significantly between treatment groups ($t = 1.43$, $df = 19$, $P = 0.170$, 95% CI of mean difference = –4.56, 0.86).

Table 6 presents exploratory correlation analyses to examine the association between UE motor performance on the FM and GPT and number of stroke-hemisphere sites where motor responses of the affected hand were evoked. Correlations are presented at baseline and follow-up for all patients (i.e., combined over treatment groups) and for each treatment group separately. As in the preliminary study,[9] a positive correlation was found in the combined sample between improvement in UE motor function on the FM and increase in the number of active TMS sites in the affected hemisphere. FM scores correlated significantly with the number of sites on the stroke hemisphere at which responses of the affected hand were evoked by TMS before treatment and at follow-up. The right-hand column of Table 6 presents the longitudinal correlations between changes in each variable, measured as the difference from baseline to follow-up. A significant positive longitudinal correlation was found in the combined sample between improvement in the FM score and increase in the number of stroke-hemisphere TMS activation sites.

The same correlations were computed within each treatment group to evaluate if the association between changes in TMS activations and motor function differed as a function of treatment. It should be noted that these results are exploratory and based on small samples. As seen in Table 6, all the within-group correlations with the FM were in the predicted direction but were stronger in the patients who had received CIMT. Table 6 also presents correlations between number of TMS active sites and motor performance on the GPT. No significant correlation was found in the combined sample. However, the within-group results suggest that correlations between GPT performance and TMS activation sites were stronger among the CIMT patients.

DISCUSSION

The main results of this study are, 1st, that long-term improvement in motor function of the affected UE did not differ significantly between patients who received CIMT and those who received traditional therapy at the same frequency and duration, and 2nd, that motor improvement was related to enlargement of the area of cortical excitability. On all measures of motor function of the affected arm and hand, patients who received CIMT showed an apparent advantageous trend over patients who received intensive traditional therapy. Relative to the control group, the CIMT group reported significantly greater improvement in quality of performing daily activities using the affected hand. In addition, on one test of motor performance by the affected UE (FM), they demonstrated significantly better improvement over the 2-week treatment period. However, no other comparisons showed a statistically significant between-group difference in motor function of the affected UE, including improvement on the FM from baseline to follow-up, which was the primary endpoint. Therefore, as an evaluation of the relative effectiveness of CIMT in early stroke rehabilitation, as compared to traditional interventions provided at the same frequency and duration, the results are overall neutral but contain some encouraging trends.

Rehabilitation therapy plays an important role after stroke, yet evidence for the effectiveness of early rehabilitation interventions including CIMT is limited. In the one previous randomized controlled trial of CIMT during early stroke rehabilitation, Dromerick et al[7] reported that patients who received CIMT demonstrated better motor performance relative to a traditional therapy group when assessed immediately after treatment. Similar to our findings, they reported greater improvement by the CIMT group on all motor function measures, including motor performance and activities of daily living, but the advantage was statistically significant on only 1 subscale of the Action Research Arm Test.[18]

The consistency of our motor performance results and their similarity with previous findings support the interpretation that the present study was underpowered to detect a relative therapeutic advantage of CIMT as compared to a control intervention provided at equal frequency and duration. On the basis of the unusually positive results observed in the preliminary phase of this study,[8,9] we probably overestimated the effect size of CIMT relative to traditional therapy and projected a sample size for the present study that was too small. In retrospect, it appears that the projected between-group difference of 14.5 points on the FM was too optimistic and that the study was not adequately powered to detect a smaller but more plausible treatment effect. The differential effect of CIMT on motor improvement observed in the preliminary study, with statistically significant advantages for the CIMT group on most measures, was not confirmed in the completed study. Although greater proximal weakness was observed in the preliminary study sample, this discrepancy could have been due to random differences between small groups.

Unfortunately, recruitment of a sample size adequate to detect a small to medium effect size was not possible at our single center. The main limitation on recruitment was that our entry criteria excluded most patients admitted to our stroke unit. Ro et al,[9] in the preliminary phase of this study, reported that fewer than 5% of stroke admissions had qualified for randomization and determined that the major exclusion was for motor impairment less severe than allowed by the NIHSS arm motor score criterion. Our exclusion of patients without detectable shoulder weakness (i.e., NIHSS arm motor score = 0) was based on the expectation that such patients would recover full UE motor function without intensive rehabilitation. However, the UE motor performance test results at 3 months after stroke (Table 2) demonstrate that most study patients achieved less than full recovery and suggest that less impaired patients could also have benefited from therapy.

This study extends previous findings demonstrating an association between TMS motor map changes and motor recovery during the initial months after stroke. The longitudinal study design, with assessment of motor performance and TMS activation area at the same time-points before and after treatment, revealed a positive relationship between extent of hand motor recovery, as measured by the FM, and the number of scalp positions over the stroke hemisphere at which motor responses of the affected hand could be evoked. An important consideration in interpreting this finding is that because the proportion of patients exhibiting evoked motor responses in the stroke hemisphere increased dramatically over the study period, the apparent association between improved motor function and increased map size could have come about because of the relationship between spontaneous motor recovery and ability to elicit motor-evoked potentials (MEPs). An additional and unexpected finding was that the association between increased TMS activations and motor recovery tended to be stronger in patients who had received CIMT, relative to the traditional therapy group. Although this finding might suggest that the association was facilitated by CIMT, this interpretation is preliminary because the analyses were exploratory and based on small samples. In addition, the significant correlation between FM performance and TMS activation sites at baseline suggests that the association may have been preexisting rather than a result of therapy.

Our TMS results are consistent with those of previous longitudinal studies[19,20] of motor recovery in chronic patients who were assessed beginning 2 or more months after stroke. Recently, Platz et al,[21] in a trial of stroke rehabilitation, demonstrated that medial shift of the motor map was associated with motor improvement. A positive association between poststroke motor function and TMS activation area has also been reported in cross-sectional studies.[22] These longitudinal results indicate that TMS map-size enlargement signals at least one mechanism through which cerebral reorganization participates in motor recovery. Interpretation of map-size enlargement is problematic because changes in map size reflect alteration in motor cortical output excitability and can be explained by different mechanisms. It has been suggested that TMS motor map enlargement could be due either to participation of additional neurons in muscle activation or to increased excitability of the motor representation by stimulation of the surrounding cortical area.[23] Our results do not clearly support either explanation, and it remains unclear whether stroke rehabilitation studies can distinguish between these mechanisms, for example, by administering TMS before and after therapy sessions.[20] Explanations of TMS map enlargement during stroke recovery need to account for use-dependent plasticity, as shown by the fact that map enlargement can be produced by rehabilitation interventions that are instituted more than 6 months after stroke.[24-27]

The experimental design of our study is relevant to methodological issues that are increasingly recognized in rehabilitation research. First, our study and that of Dromerick et al[7] were designed so that treatment groups were balanced for frequency and duration of intervention. The rationale for this design was to prevent confounding type of intervention with time spent in therapy, as would have occurred if intervention had been provided to the control patients for fewer hours or days than to the CIMT group. In that case, an advantage of CIMT over traditional therapy could have been attributed either to a different type of therapy or to greater time spent in intervention. As a consequence of balancing frequency and duration of intervention between

treatment groups, our design compared CIMT to a control condition that received more hours of therapy than is typically provided. Therefore, the results of this study should not be interpreted as a comparison between CIMT and traditional UE therapy when provided at the customary frequency of up to 1 or 2 h per day. Greater experimental control could have been achieved by inclusion of a 2nd control group that received traditional therapy at the customary frequency, or by a factorial design investigating the interaction of therapy type and hours of therapy time. However, the necessary increase in recruitment would not have been feasible at our single center. A 2nd issue in our study design is the comparison of an experimental treatment such as CIMT to a control group receiving standard or traditional therapy. If the standard therapy is not provided according to an explicit protocol and does not have its own evidence base, then the treatment condition is less easily replicated or compared among centers.[28] Measures of therapy process (e.g., time spent performing activities with the affected UE, compliance in mitten wear) could improve specification of treatment conditions and improve comparability between studies. Finally, a methodological issue in trials conducted during the subacute stage after stroke is that effects of therapy are confounded with spontaneous changes in motor function and brain organization. Spontaneous recovery probably occurred to a greater extent in our patients who were studied and treated fairly soon after stroke onset, as compared to studies in which patients were treated in the chronic stage. Although spontaneous recovery should have occurred equally between the randomized groups, such recovery could dilute a treatment effect so that further improvement due to intervention would be limited because of ongoing recovery. An additional implication is that our finding of an association between motor improvement and increased TMS activation sites may be largely due to spontaneous recovery and that it may not be possible to detect a supplementary effect of treatment on this association.

Our study and previous ones[7,9] demonstrate that implementation of a modified form of CIMT during early stroke rehabilitation is safe and feasible. No significant adverse events occurred during the treatment period, and no loss of motor function caused by restraint of the unaffected hand could be detected. Therefore, available evidence in human stroke patients undergoing CIMT does not bear out the potential adverse consequences of early overutilization of the affected limb as seen in animal studies.[29] It is possible that earlier restraint placement[29] and other procedural differences in animal studies account for the discrepant results. The frequency of 3 h of UE therapy per day as provided in our study is greater than the 2 h per day provided by Dromerick et al[7] but less than the 6 h per day used in earlier clinical trials with chronic stroke patients.[1,2] Recent clinical trials involving chronic stroke patients suggest that CIMT remains effective when provided less than the daily regimen of 6 h used in earlier studies.[4,6] The 2-week treatment duration used in this study, which is identical to most previous clinical trials of CIMT, could not be completed during the in-patient rehabilitation stay and required that patients return to complete the therapy sessions on an out-patient basis.

Limitations of our study, in addition to small sample size and design issues discussed above, include attrition and incomplete motor data on a subset of patients. This speaks to the difficulty in accurately obtaining a large amount of motor data in patients who are often uncooperative or unable to carry out many of the functions tested and who are dependent on other family members, friends, or health care workers for arranging their long-term care, transportation, and living arrangements. This makes planning of follow-up visits problematic. A 2nd limitation, which is especially salient in the acute stroke population, is the exclusion of a high proportion of patients because their motor function was too severely impaired to participate in training with the affected limb or because motor function had recovered to a level above the range specified for CIMT. A 3rd limitation is that the study could have been powered to detect an improvement in motor function that was defined as clinically important, although this remains to be defined for the motor tests used in this study. Fourth, accuracy of TMS motor mapping may have been decreased by using a polyphasic stimulator, by recording from the APB, by defining the motor threshold on the basis of only 5 trials, by using visual inspection, and by not controlling the order of TMS and behavioral motor testing. Although visual inspection could have been prone to larger errors of measurement, particularly because TMS-evoked responses in stroke patients are likely to be smaller and less visible, our preliminary study[9] found that correspondence between visual inspection and EMG was high. Moreover, inaccuracy of TMS maps would not explain the increase in TMS map size over the study period or its association with motor improvement. Although sampling at 1 kHz leaves open the possibility of aliasing error, this issue probably did not affect the results, because only noise is likely to be affected by the aliasing and MEP signal power is mostly in lower frequencies. Finally, although there are potential limitations to replacing missing data at follow-up by carrying forward the posttreatment observation, this procedure allowed an intent-to-treat analysis and would not be expected to introduce bias.

The completion of this study without adverse events combined with the encouraging trends provides a rationale for further evaluation of CIMT for subacute stroke. However, the difficulties in carrying out this study argue

for refinement of eligibility criteria and the need for a multicentered approach to increase sample size. Recruitment and retention of the necessary sample size are likely to be serious obstacles to future therapy trials for subacute stroke, particularly if the eligibility criteria are restrictive and if enrollment is limited to a single center. Inclusion in the experimental design of an additional control group, given conventional therapy at the typical number of hours per day, is needed to distinguish the effects of type of intervention from the frequency and duration of therapy. Potential predictors of therapeutic response, including baseline motor status, need to be investigated prospectively. Functional brain imaging of stroke patients in randomized controlled trials of rehabilitation therapies could improve understanding of neurophysiologic mechanisms underlying recovery and therapeutic improvement.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grants R24HD39629 (Western Medical Rehabilitation Research Network; Principal Investigator: Marjorie E. Anderson) and P50NS044227 (University of Texas Specialized Program in Acute Stroke; Principal Investigator: James C. Grotta). We are grateful to Mary Nowak for help in manuscript preparation.

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