The EXCITE Stroke Trial
Comparing Early and Delayed Constraint-Induced Movement Therapy

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Background and Purpose—Although constraint-induced movement therapy (CIMT) has been shown to improve upper extremity function in stroke survivors at both early and late stages after stroke, the comparison between participants within the same cohort but receiving the intervention at different time points has not been undertaken. Therefore, the purpose of this study was to compare functional improvements between stroke participants randomized to receive this intervention within 3 to 9 months (early group) to participants randomized on recruitment to receive the identical intervention 15 to 21 months after stroke (delayed group).

Methods—Two weeks of CIMT was delivered to participants immediately after randomization (early group) or 1 year later (delayed group). Evaluators blinded to group designation administered primary (Wolf Motor Function Test, Motor Activity Log) and secondary (Stroke Impact Scale) outcome measures among the 106 early participants and 86 delayed participants before delivery of CIMT, 2 weeks thereafter, and 4, 8, and 12 months later.

Results—Although both groups showed significant improvements from pretreatment to 12 months after treatment, the earlier CIMT group showed greater improvement than the delayed CIMT group in Wolf Motor Function Test Performance Time and the Motor Activity Log (P < 0.0001), as well as in Stroke Impact Scale Hand and Activities domains (P < 0.0009 and 0.0214, respectively). Early and delayed group comparison of scores on these measures 24 months after enrollment showed no statistically significant differences between groups.

Conclusions—CIMT can be delivered to eligible patients 3 to 9 months or 15 to 21 months after stroke. Both patient groups achieved approximately the same level of significant arm motor function 24 months after enrollment.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00057018. (Stroke. 2010;41:2309-2315.)

Key Words: constraint-induced movement therapy ■ forced use ■ rehabilitation ■ stroke ■ upper extremity

Americans continue to experience >780,000 strokes each year, with total costs for care and management estimated at $65.5 billion in 2008 and two-thirds demonstrating impaired function in upper extremity usage.1 Rehabilitation regimens emphasize functional retraining for these stroke survivors.2 Constraint-induced movement therapy (CIMT) requires restraint of the less impaired upper extremity through the use of a padded mitt that restricts hand usage and is coupled with behavioral training (repetitive and adaptive task practice) for up to 6 hours per day.3

The Extremity Constraint Induced Therapy Evaluation (EXCITE) Trial was the first multisite, randomized, controlled study of a nonsurgical or pharmacological procedure applied to patients 3 to 9 months after stroke.4 We found that in comparison to a group receiving customary care only, those undergoing 2 weeks of CIMT showed significantly greater improvement5 that persisted through another follow-up year.6 The control group subsequently was crossed-over to receive CIMT 1 year after enrollment. In this article, we report the extent to which improvements in functional recovery after CIMT among this more chronic group (15 to 21 months after stroke) would compare to those already reported for participants receiving CIMT within 3 to 9 months after stroke.5

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Patients and Methods

Study Population
Between January 2001 and January 2003, 222 participants were randomly assigned to receive CIMT either at enrollment (earlier CIMT [E-CIMT], $n=106$) or after a 1-year delay (delayed CIMT [D-CIMT], $n=116$). Participants were recruited if they had sustained a stroke 3 to 9 months before recruitment, could stand from a sitting position, could remain standing for at least 2 minutes without support, and satisfied all inclusion criteria, including initiation of active extension of the wrist and fingers. Patients were excluded if they were receiving or intended to receive pharmacological management of spasticity, had terminal diagnoses, were cognitively impaired, or intended to relocate. Specific joint passive ranges of motion and the Fugl-Meyer Upper Extremity Assessment, a commonly used 66-point scale to determine upper extremity synergy, were measured.

CIMT
CIMT uses a padded safety mitt worn on the less-impaired upper extremity during 90% of waking hours over the 2-week CIMT training interval. Laboratory-based training was performed over 10 consecutive days and consisted of 6 hours of monitored behavioral shaping and repetitive task practice, selected from >60 tasks using only the impaired limb with the actual mean time of training within the laboratory. Actual training time increased with patient endurance, ranging from 1.5 hours on the first day to 4.5 hours on the last day. The mitt was only worn during the 2-week training interval after randomization (E-CIMT) or 1 year later (D-CIMT).

Adherence to mitt use was high in the laboratory environment and reinforced in the home through daily “homework” behavioral contracts for both the patient and the caregiver, and a mitt compliance device that measured hand contact time within the mitt. The device was a contact plate that measured time of hand contact. The time output was continuously updated to a microprocessor housed within the mitt. The less affected limb was free to move to protect from loss of balance. During the training period, participants wore the mitt at home and the contact time was recorded and used as a surrogate for unimanual activity. Because of technical problems, the performance data are only available for a subset of participants undergoing training, but no differences between E-CIMT and D-CIMT groups were found.

Study Design
The EXCITE Trial was a masked crossover design. After enrollment, the E-CIMT participants underwent 2 weeks of CIMT therapy (follow-up evaluations for 23.5 months). The D-CIMT participants received CIMT therapy after 12 months (follow-up evaluations for 11.5 months). D-CIMT participants could seek any rehabilitative therapy except CIMT during the treatment delay year after study enrollment. Information about these therapies was documented, but neither the quality nor the quantity was ascertained. All participants were administered primary outcome assessments every 4 months after randomization (baseline–Pre1; 0.5 month–Post1; 4 month; 8 months; 12 month–Pre2; 12.5 month–Post2; 16 month; 20 month; 24 month). Some measures were not administered at every visit.

Outcome Measures: Wolf Motor Function Test
The Wolf Motor Function Test (WMFT) consists of 15 time-based and 2 strength items sequenced from requiring use of more proximal upper extremity joints to more complex tasks requiring more upper extremity joints and fine motor skills and allowing a maximum of 120 seconds per timed item completion. All items were videotaped and subsequently scored on a 6-point quality of movement scale, called the Functional Ability Scale, by trained raters masked to group assignment and session. This scale rates the task from not being initiated through assistive use of the less impaired upper extremity to independent normal motion. Functional level refers to the amount of active wrist and finger extension demonstrated during 3 repetitions of active movement performed over 1 minute. Extension of all wrist and all digits by at least 20 degrees from a resting gravity-eliminated position or the ability to extend the wrist, thumb, and 2 additional digits by 10 degrees over the same time interval defined higher and lower functional levels, respectively. Properties of the WMFT have been previously published.

Motor Activity Log
The Motor Activity Log (MAL) is a structured interview containing 30 activities of daily living (ADL) items administered independently to participants who rated each item on an 11-point scale for quality of movement and for amount of use of the paretic limb. The MAL exhibits good convergent validity ($r>0.68$) and has been validated with the hand function domain of the Stroke Impact Scale (SIS) and with accelerometer measurements.

SIS
The SIS, a secondary outcome measure, is a comprehensive, health status patient report that measures changes in a summary measure and 8 subdomains of impairment, function, and quality of life, including strength, memory, emotion, communication, ADL, mobility, hand function, and participation.

Defining Clinically Important Improvements
Clinically important improvement was defined as a change in the number of WMFT tasks that could be completed (<120 seconds) after CIMT treatment. A score of $\geq 3$ on both the quality of movement and amount of use MAL provides the first indication of ADL item initiation without use of the less impaired limb. Therefore, the change in number of MAL items that are rated $\geq 3$ after CIMT was also assessed.

Statistical Analysis
The effects of CIMT on functional outcomes between E-CIMT and D-CIMT groups were compared in the year after treatment. An intent-to-treat plan was used so that all data were included in analyses. The main analysis was a mixed-effects repeated-measures analysis (SAS PROC MIXED; SAS). Factors included treatment group (E-CIMT or D-CIMT), functional ability (high or low, based on active wrist and finger motion) as between-subject factors, and evaluation time point as a within-subject repeated-measure variable. Least-squares means, used to ensure that missing values did not distort means and to incorporate covariate adjustments in the means, were computed for each separate evaluation for each group. The WMFT items are timed, with shorter times indicating better performance, and were analyzed using log-transformed values (back-transformed values are presented for interpretability). For count variables, Poisson-link Generalized Estimating Equation (GEE) models were used. Specific comparisons were tested using preplanned contrasts. These included comparisons of pretreatment and post-treatment values (to assess treatment effect), pretreatment to 12 months post-treatment values (to assess persistence of treatment), change from before 1 year to before 2 years for the D-CIMT group (to examine natural, nonspecific changes), and difference between intervention and nonintervention intervals for the D-CIMT group. All queries were prespecified and performed at the nominal significance level of $\alpha=0.05$. A Bonferroni-adjusted test was used to evaluate a posteriori comparisons and interactions between covariates (gender, concordance [agreement of hemiparetic upper extremity side with prestroke dominant side], and functional level), with a corrected $P=0.05/18=0.0028$. Statistical analyses were validated by last observation carried forward methods (results are equivalent and not presented).

Results

Study Population
At randomization, there were 106 E-CIMT (mean time poststroke, 178±64 days) and 116 D-CIMT (mean time poststroke, 187±67 days) participants, 86 of whom received...
treatment. Participant loss is shown in the CONSORT diagram (Figure 1).

**D-CIMT Before Treatment**

During the year after randomization, 24% (21/86) of D-CIMT participants received some form of therapy.7 There were no significant interactions for the WMFT ($P=0.25$) or the MAL amount of use ($P=0.99$), or the MAL quality of movement ($P=0.73$) between these D-CIMT subgroups. This “external treatment” factor was ignored for other analyses. D-CIMT participants showed significant improvement on the WMFT, MAL scores including the number of tasks scored as $\geq 3$, and the SIS Meaningful Activities and Typical Activities subscales (Tables 1 and 2; D-CIMT, Pre1 vs Pre2). Collectively, these results suggest that D-CIMT participants experienced some recovery before receiving CIMT. Although 30 D-CIMT subjects withdrew from the EXCITE trial before the training period (Figure 1), there were no prerandomization differences in any demographic variables measured between those who withdrew from the trial and those who started training (results not shown).

**Within-Group Improvements**

Both groups improved significantly with treatment for primary outcome variables (Table 1; E-CIMT, Pre1 vs Post1; D-CIMT, Pre2 vs Post2). Similar improvements were seen 12 months after treatment (Table 2; E-CIMT, Pre1 vs Pre2; D-CIMT, Pre2 vs 24 months). These improvements are shown graphically for the WMFT and the MAL amount of use (Figure 2A, 2B) and indicate that D-CIMT participants can achieve a level comparable to E-CIMT participants. Differences after training between values at time points were assessed between groups. These tests were not significant, indicating that only minor differences between groups occurred after training (results not shown). Tests comparing results for time points separately for each group were not significant using Bonferroni-corrected tests (results not shown).

**Between-Group Differences**

There were no differences in patient demographics between groups when they were initially randomized.5 Several significant between-group differences were found between the E-CIMT before month 1 data and the D-CIMT before month 2 data (Table 1), including log mean WMFT time, WMFT functional ability, weight, grip, MAL scores including the number of tasks scored as $\geq 3$, and the SIS Hand Function and ADL/instrumental ADL (meaningful) subscales, reflecting improvement in function in the D-CIMT group over the year-long delay.

Table 2 presents the least-squares means for all primary and secondary outcome measures for the time points relative to the year of intervention. For the E-CIMT group, before month 1, after month 1, and before month 2 values are shown,
whereas comparable time points are shown for the D-CIMT group (4-month, 8-month, 16-month, and 20-month values are omitted from the table for simplicity). The primary test of the null hypothesis of no difference over time between groups adjusted for functional level is also presented (Table 2, Interaction). This test compares the results 12 months after baseline between groups while adjusting for the pretraining level. The WMFT (all components except weight), MAL (all components), and the SIS 7 hand function domain all show a significant improvement over time compared to the E-CIMT group’s SIS 8 ADL/instrumental ADL (P<0.0001), and improvements for the E-CIMT group’s SIS 8 ADL/instrumental ADL were marginally significant (P=0.0507). A subsequent analysis that examines differences between the groups 24 months after enrollment (Table 1, column 3) indicates no significant differences between the groups.

### Table 2. Effect of Constraint-Induced Movement Therapy on Primary and Secondary Outcome Measures

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>E-CIMT</th>
<th>D-CIMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>After Rx</td>
</tr>
<tr>
<td>WMFT mean time (sec)</td>
<td>30.0†</td>
<td>19.9‡</td>
</tr>
<tr>
<td>Functional Ability Scale score</td>
<td>2.38</td>
<td>2.67</td>
</tr>
<tr>
<td>WMFT N tasks &gt;120</td>
<td>2.17</td>
<td>0.93†</td>
</tr>
<tr>
<td>MAL AOU</td>
<td>1.13‡</td>
<td>2.29†</td>
</tr>
<tr>
<td>MAL QOM</td>
<td>1.20†</td>
<td>2.24‡</td>
</tr>
<tr>
<td>% MAL AOU tasks &gt;3</td>
<td>17†</td>
<td>45‡</td>
</tr>
<tr>
<td>% MAL QOM tasks &gt;3</td>
<td>21†</td>
<td>48‡</td>
</tr>
<tr>
<td>SIS 4 communicate</td>
<td>83.7</td>
<td>88.7</td>
</tr>
<tr>
<td>SIS 5 activity</td>
<td>61.0</td>
<td>69.6</td>
</tr>
<tr>
<td>SIS 7 hand function</td>
<td>25.6*</td>
<td>49.8‡</td>
</tr>
<tr>
<td>SIS 8 ADL/IADL</td>
<td>49.3‡</td>
<td>63.4</td>
</tr>
<tr>
<td>SIS 9 dominant side</td>
<td>56.7</td>
<td>65.6</td>
</tr>
</tbody>
</table>

ADL indicates activities of daily living; AOU, amount of use; B, baseline; D, delayed; D-CIMT, delayed constraint-induced movement therapy; E, early; E-CIMT, early constraint-induced movement therapy; IADL, instruments of activities of daily living; Post1, after month 0.5; Post2, after month 12; Pre1, before 1 month; Pre2, before month 12; QOM, quality of movement; WMFT, Wolf Motor Function Test.

*P < 0.05.
†P < 0.01.
‡0.01 < P < 0.05.
§P = 0.001.
differences on the WMFT and both MAL measures. In the SIS hand function, ADL/instrumental ADL, and communication domains, however, the E-CIMT group reports significantly higher function than the D-CIMT group (means for the E-CIMT group at 24 months are not shown).

No demographic or baseline characteristics predicted study withdrawal during the year after treatment. Withdrawal after treatment was examined using logistic regression and for time to event (Cox regression). Using Bonferroni-corrected probability values, no predictor was significant for either method.

Covariate Analyses
For 3 important variables (gender, concordance, and functional ability), the 3-way interactions between treatment, evaluation, and covariate were examined for outcome variables. Using Bonferroni-corrected tests, 1 interaction was significant (functional level for variable MAL quality of movement; results not shown).

Clinically Important Improvements
The ability to successfully complete tasks in the WMFT and use the affected upper limb in everyday activities (rating of MAL items ≥3) was considered evidence of clinically important improvements (Table 2). The E-CIMT condition showed larger improvements in WMFT completion (E-CIMT, −0.89; D-CIMT: −0.20), amount of use/MAL ≥3 (E-CIMT, 26; D-CIMT, 8), and quality of movement/MAL ≥3 (E-CIMT, 28; D-CIMT, 8). All interactions are significant (Table 2), indicating that the change for the E-CIMT group is larger than that for the D-CIMT group.

Safety
Severe adverse events occurring during the first year were presented previously. From before month 1 to before month 2, E-CIMT participants experienced 2 deaths and 14 severe adverse events. During the interval before month 2 to 24 months, D-CIMT participants sustained 1 death and 10 individual severe adverse events hospitalizations (emphysema, internal bleeding, second stroke, cancer, congestive heart failure, subdural hematoma, hypertension, chest pain, hip arthroplasty, 2 fractures). None of those events was related to the intervention. In a generalized linear model that controlled for the repeated events within individuals, comparison of adverse event rates between groups showed no statistically significant difference (P=0.58).

Discussion
Until now, to our knowledge, there has been little to no level I evidence to inform the hypothesis that earlier CIMT is better than later CIMT evidence. Evidence from other animal and human stroke studies suggest that limb rehabilitation within days of a stroke may be detrimental to recovery. Some studies indicate CIMT delivered to chronic stroke survivors resulted in far more substantial improvements than those seen in acute patients.

In the EXCITE Trial, patients responded favorably to CIMT. Although both groups improved, those participants receiving treatment within 3 to 9 months after stroke demonstrated significantly greater changes from immediately before to 12 months after treatment. This finding supports other studies showing that rehabilitation applied sooner during the recovery phase results in a faster rate of change; however, increasing CIMT from 2 to 3 hours per day applied within a few days after stroke does not necessarily produce superior outcomes. Functional improvements after CIMT have been associated with cortical plasticity as mapped using transcranial magnetic stimulation to motor cortex, functional MRI including a subset of EXCITE participants, and MRI; the extent to which the magnitude of reorganization is influenced by relative chronicity is undergoing investigation. To date, structural reorganization associated with early training has been characterized by maintenance of the original focus of motor control (primary motor cortex); however, training in the chronic phase was characterized by increases...
in bilateral sensory-motor, premotor, and hippocampal activity. Recovery in the chronic state may be influenced by the loss of hand and expansion of nonhand representation areas within the primary motor cortex during the delayed period that contribute to atypical movement patterns and compete with subsequent neural reorganization during later training periods, resulting in smaller treatment effects in the chronic vs the acute periods as seen in this study.

The actual time to complete laboratory tasks (WMFT) and the perceived amount and quality of limb use in home-based activities (MAL) improved, as did the often neglected quality of life in hand function and ADL/instrumental ADL SIS domains. More significantly, the percentage of WMFT tasks that could be completed substantially improved in both groups (31% and 8%, E-CIMT and D-CIMT, respectively). Taken together with the percentage of real-world activities that could be completed using the impaired limb independently (MAL >3), both groups showed functionally meaningful gains but with a more profound improvement noted in the E-CIMT group. Similar to findings from our first-year analyses, these chronicity effects were not affected by functional level (amount of active wrist and finger range of motion), concordance, or gender.

The most apparent and likely biggest factor for the greater treatment effect in early vs late is the discrepancy in when each group began the intervention. Although a subset of D-CIMT received other interventions during the year before CIMT, this did not affect the amount by which they improved. The improvement seen in the D-CIMT group when exposed to CIMT 1 year later speaks to the potency of this approach but CIMT accounts for some, although not all, of this improvement. The possibility that the quarterly evaluation visits alone may have focused attention on paretic limb use during the no-training interval cannot be ruled out.

The D-CIMT group showed improvements during the year of no training as evidenced by pre-CIMT outcome measures that were actually better than before month 1 measures in the E-CIMT group (Figure 1). The magnitude by which this chronic group could improve after CIMT might well have been limited by the extent of which they could improve or the extent to which our outcome measures were sensitive to improvements resulting from continued efforts to use the limb during the postenrollment interval; changes in motivation; limitations in motor control caused by persistence or changes in muscle tone or strength; alterations in self-perception of the potential for limb use; or neuroplastic reorganization of the sort mentioned. Furthermore, when considering the improvement by the D-CIMT group in the year before CIMT plus the year after CIMT (ie, outcome 24 months after enrollment), D-CIMT outcomes on the WMFT and MAL are similar to those for E-CIMT at the same time point. Therefore, although one can conclude from the data that CIMT produces improvement in motor measures that are greater when administered 3 to 9 months after stroke compared to 1 year later, our data also suggest that comparable results for both groups may occur after the full period of training and evaluation. In fact, both groups demonstrated significant gains at the end of their respective 10 sessions CIMT and then maintain these gains throughout the subsequent year.

Conclusion

Results from this trial and other investigations into the “signature” CIMT developed by Taub raise several issues. In addition to uncertainties about the optimal delivery and intensity of CIMT training, alternative forms of delivery using distributed rather than intense blocked practice models need to be explored. For example, small scale studies by Page and Wu offer the potential for comparable results with less intense individualized training. However, the optimal modification of CIMT needs to be defined first, followed by a direct comparison to the present mode using a large enough sample size to undergo the rigors of an intention-to-treat analysis.

The results from this study show that the improvements persist, and none of the severe adverse events was related to CIMT. However, the percent of stroke survivors who meet our inclusion criteria ranges from 5% to 23%, based on how the degree of impairment is defined. Inevitably, the prospects for bolstering the value of this intervention for a larger population of patients may reside in better understanding of the causal and nonlinear relationships between limb function and daily use that will only emerge from proper translational research at both the theoretical and practical levels.

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Disclosures

None.

References


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