A Placebo-Controlled Trial of Constraint-Induced Movement Therapy for Upper Extremity After Stroke

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Background and Purpose—Constraint-Induced Movement therapy (CI therapy) is a neurorehabilitation technique developed to improve use of the more affected upper extremity after stroke. A number of studies have reported positive effects for this intervention, but an experiment with a credible placebo control group has not yet been published.

Methods—We conducted a placebo-controlled trial of CI therapy in patients with mild to moderate chronic (mean=4.5 years after stroke) motor deficit after stroke. The CI therapy group received intensive training (shaping) of the more affected upper extremity for 6 hours per day on 10 consecutive weekdays, restraint of the less affected extremity for a target of 90% of waking hours during the 2-week treatment period, and application of a number of other techniques designed to produce transfer to the life situation. The placebo group received a program of physical fitness, cognitive, and relaxation exercises for the same length of time and with the same amount of therapist interaction as the experimental group.

Results—After CI therapy, patients showed large (Wolf Motor Function Test) to very large improvements in the functional use of their more affected arm in their daily lives (Motor Activity Log; P<0.0001). The changes persisted over the 2 years tested. Placebo subjects showed no significant changes.

Conclusion—The results support the efficacy of CI therapy for rehabilitating upper extremity motor function in patients with chronic stroke. (Stroke. 2006;37:1045-1049.)

Key Words: controlled clinical trials • rehabilitation • stroke • treatment outcome

At present, there is little experimental evidence available indicating that physical rehabilitation is effective for patients with chronic stroke; the prevailing view has been that the amount of motor recovery present at 1 year after stroke is the level at which patients will remain.1 The literature is even equivocal on the value of rehabilitation for subacute patients.1 However, preliminary studies from this laboratory have provided data that Constraint-Induced Movement (CI) therapy can produce a large improvement in the amount of use of the more-impaired arm in patients with chronic stroke.2–4 These results have been replicated in studies from other laboratories.5 This improvement is of interest because it is reported to transfer to the life situation and persist for ≈2 years.

The treatment used here differs from conventional physical rehabilitation in its duration and intensity. It involves training of the more affected extremity by shaping for 6 hours per day over consecutive weeks while constraining use of the less affected extremity for the majority of waking hours during this period to induce increased use of the more affected limb. In addition, several techniques are used to achieve transfer of improved motor function to the life situation. The treatment was derived from research with monkeys5 and may be considered 1 of a new class of neurorehabilitation techniques founded on basic research in neuroscience and behavioral science that give promise of efficacy.6

There are >120 published studies using either the original technique or, in many cases, a variant. The magnitude of the treatment effect has varied, but all studies report a positive outcome. However, a major barrier to the resolution of doubt concerning the technique is the absence of a study with a credible placebo control group. We report such a study here.

Methods

Participants

Individuals with chronic stroke were recruited mainly by advertising in periodicals. Respondents were screened using structured telephone interviews and then structured examinations by a physical therapist and a neurologist or physiatrist. Eligible individuals were assigned to either a CI therapy (n=21) or placebo control group (n=20). The 2 groups were matched on initial motor deficit by assigning participants to each group in blocks on the basis of scores

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Interventions

The CI therapy group received both components of a published protocol derived from the work with deafferented monkeys (ie, paretic arm training and contralateral arm restraint). The training was administered intensively for 6 hours per day with an additional hour of interpolated rest on each weekday of the 2-week treatment period. The training consisted primarily of a procedure termed shaping (supplemental Appendix I, available online at http://stroke.ahajournals.org). which involved: (1) quantifying and very frequent immediate feedback concerning improvements in the speed and quality of movement (QOM), (2) selecting tasks that were tailored to address the motor deficits of the individual patient, (3) modeling, prompting, and cuing of task performance, and (4) systematically increasing the difficulty level of the task performed in small steps when 5 trials of improved performance occurred. The CI therapy participants also wore a resting hand splint/sling ensemble on their less affected extremity that prevented use of that arm for a target of 90% of waking hours for the entire 14-day treatment period. The rationale was to promote use of the more affected arm outside the laboratory when safety permitted. Additional behavioral techniques, such as behavioral contracts and problem solving (supplemental Table I, available online at http://stroke.ahajournals.org) were used to facilitate transfer of treatment gains from the therapeutic to the home setting.

The placebo control group was designed to control for the duration and intensity of patient–therapist interactions and therapeutic activities. These participants received a general fitness program in which they performed strength, balance, and stamina training exercises, played games that provided cognitive challenges, and practiced relaxation exercises for 6 hours per day for 10 consecutive weekdays. Their answers to a laboratory standard questionnaire about their expectations before the intervention (Table 1) suggests that they found the control treatment to be credible.

Measures

Treatment outcomes were assessed in the domain of real-world arm use and arm motor ability. The MAL is a structured interview that measures how well (11-point QOM scale) and how much (11-point amount of use [AOU] scale) patients use their more impaired arm in their life situation for accomplishing 14 activities of daily living (supplemental Appendix II, available online at http://stroke.ahajournals.org). Analyses indicate that it is a reliable, stable, and valid measure of real-world arm function. Expectations of improvement (5-point QOM scale) and how well (5-point QOM scale) patients use their more impaired arm in their daily lives. Patients are videotaped without their awareness (but after previous agreement to permit videotaping) while they are guided through a standardized scenario that includes 17 activities that afford an opportunity to use their more impaired arm. Trained masked observers evaluate how much (2-point AOU scale) and how well (5-point QOM scale) patients use their more impaired arm from videotape. Only the QOM or arm use score is reported because scores from the 2 scales were redundant (pretreatment and post-treatment rQOM, AOU >0.9; P<0.0001). The test–retest reliability of the AAUT arm use scale (r=0.76) and its convergent validity with the MAL (r=0.45; P<0.01) are adequate. The WMFT is a laboratory test of motor ability that evaluates the speed (PT) and coordination (functional ability [FA] scale) with which patients complete 14 tasks using their more impaired arm. PT is recorded live by the tester; FA is scored from videotape by trained masked observers using a 5-point scale. The WMFT has an established reliability and validity. The masked observers who rated the WMFTs and AAUTs from this study exceeded a criterion of 0.9 agreement with a benchmark set of scored videotapes before rating study data. The MAL and WMFT are considered primary measures of CI therapy outcome; the AAUT provides an objective, convergent measure of real-world arm use. Expectations of improvement and self-efficacy for following the study procedures were also assessed using a 4-item questionnaire. The schedule of testing is summarized in supplemental Table II, available online at http://stroke.ahajournals.org.

TABLE 1. Demographic, Stroke-Related, and Expectancy Characteristics of CI Therapy Patients and Placebo Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CI Therapy (n=21)</th>
<th>Control (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>54.6±12.1</td>
<td>50.7±19.2</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European-American</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>African American</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Stroke-related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresis of right side</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Paresis of dominant side</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Time since stroke, y</td>
<td>3.6±4.5</td>
<td>5.3±3.9</td>
</tr>
<tr>
<td>Between 1 and 2 y</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Between 2 and 5 y</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Between 5 to 20 y</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Expectancy (maximum=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Credibility of treatment</td>
<td>7.7±2.3</td>
<td>7.6±2</td>
</tr>
<tr>
<td>Treatment outcome expectancy</td>
<td>8.1±1.3</td>
<td>7.9±1.8</td>
</tr>
<tr>
<td>Self-efficacy for wearing restraint device</td>
<td>8.1±1.7</td>
<td>n/a</td>
</tr>
<tr>
<td>Self-efficacy for training more impaired arm</td>
<td>8.4±1.8</td>
<td>7.7±1.8</td>
</tr>
</tbody>
</table>

Values are mean±SD.
Results

Initial Differences Between Groups

There was a trend toward a significantly larger number of women in the CI therapy group than in the control group (P=0.06; Table 1). This difference was noteworthy because female CI therapy patients showed larger gains than males on the MAL (P=0.02; f=0.23): women improved 2.1±0.4 points (d'=5.3), whereas men improved 1.5±0.6 points (d'=2.5). The CI therapy group was also more racially diverse than the fitness controls (P=0.02; Table 1), and there were additional initial differences between the groups on some of the measures (arm strength, mood). However, these differences were unlikely to have influenced the findings regarding efficacy because there were no significant relationships between the initial values of these parameters and treatment gains in the CI therapy group.

Changes from Pretreatment to Post-Treatment

The CI therapy group showed very large improvements in the quality and amount of more impaired arm use outside the laboratory relative to the general fitness control group. On the MAL arm use scale, CI therapy subjects reported a mean increase of 1.8 points, whereas controls reported no change (P<0.0001; f=3.0; Table 2; Figure). The patients’ reports were corroborated by those of their caregivers (P<0.0001; f=0.8; Table 2). Furthermore, the MAL results were confirmed by the AAUT. CI therapy participants (n=15) showed an 87.5% increase on the AAUT arm use scale; controls (n=17) exhibited a 20% decrease (P=0.0003; f=0.5; Table 2). On the WMFT, CI therapy subjects showed moderate improvements in the speed with which they completed tasks in the laboratory with their more impaired arm relative to the controls. The CI therapy group (n=21) exhibited a −2.3±0.7 s decrease in PT, whereas the control group (n=18) displayed a 0.5±3.6 s increase (P=0.005; f=0.23; Table 2). On the WMFT FA scale, which measures movement quality, CI therapy subjects showed a trend toward a significant improvement relative to controls (P=0.1; f=0.08; Table 2).

Persistence of Improvements

CI therapy subjects retained the gains made in real-world arm use during treatment over the initial 4-week follow-up period (NS). The improvement in the patient MAL score (n=19) at the 4-week follow-up, relative to pretreatment, remained at 1.8±0.8, and the caregiver MAL score (n=12) remained at 1.6±1.0. Controls displayed no significant changes in their MAL scores at the 4-week follow-up period (n=18) or ≈3 months after treatment (n=16).

<table>
<thead>
<tr>
<th>Test</th>
<th>CI Therapy (n=21)</th>
<th>Placebo Controls (n = 20)</th>
<th>Differences in Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Change</td>
</tr>
<tr>
<td>Real-world outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(MAL; maximum=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm use rated by patient†</td>
<td>1.3±0.6</td>
<td>3.1±0.6</td>
<td>1.9±0.6</td>
</tr>
<tr>
<td>Arm use rated by caregiver</td>
<td>1.1±0.1</td>
<td>2.6±0.7</td>
<td>1.6±0.9</td>
</tr>
<tr>
<td>AAUT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm use scored by blinded rater†</td>
<td>0.8±0.4</td>
<td>1.5±0.9</td>
<td>0.7±0.7</td>
</tr>
<tr>
<td>Laboratory outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMFT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance time(s)‡</td>
<td>5.3±3.1</td>
<td>3±1.1</td>
<td>−2.3±2.3</td>
</tr>
<tr>
<td>Functional ability</td>
<td>3±0.4</td>
<td>3.2±0.4</td>
<td>0.2±3</td>
</tr>
</tbody>
</table>

Values are mean±SD.

* Cohen’s f is a measure of effect size (small f=0.1, medium f=0.25, large f=0.4); it indexes the magnitude of the differences between the 2 groups in preintervention to postintervention change. For each outcome, it is the variance in the relevant outcome measure accounted for by the group (CI therapy, placebo control)×time (preintervention, postintervention) interaction divided by the error variance for this factor.14

†AAUT scores were available from 15 CI therapy patients and 17 controls. The AAUT was not conducted with the first 4 participants because development of the test had not yet been completed; pretreatment or post-treatment AAUT data from 5 other subjects were missing because of videotaping errors. Subjects with and without AAUT scores did not have significant differences in arm use on the MAL at pretreatment or in pretreatment to post-treatment change on the MAL.

‡On the WMFT, the improvement in PT (f=0.23; 46%) was substantially larger than in FA (f=0.08; 6%). The relatively large gains in PT can be explained by the emphasis placed in CI therapy on the rate of performance rather than the quality of movement during training. The parameter shaped during training is typically the No. of repetitions during a fixed interval or the time to perform a fixed No. of repetitions rather than movement pattern.
At 2-year follow-up, the treatment group (n=14) showed a very large improvement on the MAL (1.0±1.1) relative to pretreatment (P<0.05; d’=0.9). Relative to post-treatment, this represented a 0.7±0.9 (23%) decrease (P<0.05; d’=0.8). Long-term follow-up was not collected from 33% of the treatment group because these patients were deceased, could not be contacted, or refused to complete testing. Similar gains at post-treatment for participants with and without 2-year follow-up suggested that these missing data did not bias the long-term follow-up results; CI therapy subjects who completed 2-year follow-up reported a 1.7±0.6 gain at post-treatment, whereas subjects who did not reported a 1.9±0.7 gain. However, it was still possible that subjects who completed 2-year follow-up showed smaller decrements in arm use over the follow-up than subjects who did not.

Relation of Treatment Change to Initial Participant Characteristics
There were no significant associations between pretreatment arm motor ability (WMFT) or real-world arm use (MAL) and gains in real-world arm use within the segment of the population with chronic stroke we worked with (ie, patients with mild/moderate motor deficit). Side of paresis, paresis of the prestroke dominant arm, chronicity, age, and race had no effect on treatment outcome.

Discussion
As in previous experiments, patients receiving CI therapy showed large to very large increases in spontaneous use of their more impaired arm in the real-world environment, as indexed by the effect size of the change in MAL scores, and moderate improvement in more-impaired arm motor ability, as shown by a laboratory motor performance test (WMFT). In contrast, patients given a credible placebo intervention did not show a significant change in either of these measures.

Van der Lee et al used a form of CI therapy that was modified in important respects (training on a group basis using “housekeeping activities, handicrafts, and games” in a relaxed atmosphere). The treatment effect reported was smaller (but still significant) than in this study, but these results are at variance with those of the other studies that have followed the protocol in our initial publication (one-on-one training, intensive approach, use of specific upper extremity tasks tailored to the motor deficits of individual patients).

A finding of interest was that female patients showed larger gains on the MAL than males. A possible explanation is that women may receive more frequent or more powerful reinforcement of more impaired arm use from their social environment than men. Another possibility consistent with recent animal studies is that differences between women and men in gonadal hormone levels might enhance therapy-induced brain plasticity in the women. Any bias introduced by the differences in gender between groups (48% versus 20% female for CI therapy versus control groups, respectively) was not large enough to alter conclusions regarding the efficacy of CI therapy. We estimated that the mean improvement among CI therapy subjects on the MAL arm use scale would be 1.7 if there were the same smaller number of women in the CI therapy group as in the control group rather than the 1.9 that was actually recorded.

CI therapy is thought to achieve its therapeutic effect by 2 linked but independent mechanisms: overcoming learned nonuse and use-dependent neural plasticity. The first mechanism was observed in the primate experiments on which CI therapy is based. When somatic sensation is surgically abolished by dorsal rhizotomy from a single forelimb in monkeys the deafferented extremity is never used. Converging evidence indicated that this nonuse is a learning phenomenon, involving a suppression of movement that develops in the early period after the central nervous system damage. This learned inhibition of movement can be overcome with techniques similar to those used in CI therapy. This research suggests that some part of the substantial deficit in spontaneous use of the more impaired arm often observed in patients with stroke, when accompanied by relatively modest deficits in more impaired arm motor ability, is attributable to learned nonuse. The rapidity with which large improvements

Mean MAL arm use scores from CI therapy (n=21) and placebo control (n=20) participants. CI therapy subjects showed a very large improvement in arm use outside the laboratory from pretreatment to post-treatment (1.8±0.6; P<0.0001; d’=3.0), whereas controls showed little change. In follow-up, CI therapy subjects retained all of their immediate treatment gains 4 weeks after therapy and showed only a 23% decrease from post-treatment levels of real-world arm use 2 years afterward.
in real-world arm use occurred in this and other studies\textsuperscript{2–4} is consistent with the lifting of a learned inhibition of movement, as observed in the course of recovery in deafferented monkeys undergoing CI therapy-like procedures. The smaller improvements in motor ability observed in CI therapy patients, as reflected in scores on the WMFT, would be accomplished on the basis of motor learning, which is typically a slower process. Evidence for this formulation and its mode of operation have been described in detail previously.\textsuperscript{2,3,5,6}

With regard to the second mechanism underlying its therapeutic effect, CI therapy has been shown to generate a large use-dependent brain reorganization in which substantial new areas of the brain are recruited into the innervation of movement of the more affected extremity. This is correlative with the large changes in function that CI therapy produces in humans after stroke and monkeys after simulated stroke and deafferentation.\textsuperscript{6} The present experiment adds the support of a placebo-controlled trial to the possibility that this activity-dependent brain plasticity can be harnessed through appropriate behavioral or rehabilitation techniques to produce a clinically meaningful therapeutic effect on chronic motor deficits after neurological damage. The traditional view that chronic stroke patients are refractory to treatment needs to be reconsidered.

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References
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