Does the Application of Constraint-Induced Movement Therapy During Acute Rehabilitation Reduce Arm Impairment After Ischemic Stroke?

Alexander W. Dromerick, MD; Dorothy F. Edwards, PhD; Michele Hahn, MS/OTR

Background and Purpose—Motor dysfunction after unilateral deafferentation in primates can be overcome by restraining the unaffected limb. We asked whether a constraint-induced movement (CIM) program could be implemented within 2 weeks after stroke and whether CIM is more effective than traditional upper-extremity (UE) therapies during this period.

Methods—Twenty-three persons were enrolled in a pilot randomized, controlled trial that compared CIM with traditional therapies. A blinded observer rated the primary end point, the Action Research Arm Test (ARA). Inclusion criteria were the following: ischemic stroke within 14 days, persistent hemiparesis, evidence of preserved cognitive function, and presence of a protective motor response. Differences between the groups were compared by using Student’s t tests, ANCOVA, and Mann-Whitney U tests.

Results—Twenty subjects completed the 14-day treatment. Two adverse outcomes, a recurrent stroke and a death, occurred in the traditional group; 1 CIM subject met rehabilitation goals and was discharged before completing 14 inpatient days. The CIM treatment group had significantly higher scores on total ARA and pinch subscale scores (P<0.05). Differences in the mean ARA grip, grasp, and gross movement subscale scores did not reach statistical significance. UE activities of daily living performance was not significantly different between groups, and no subject withdrew because of pain or frustration.

Conclusions—A clinical trial of CIM therapy during acute rehabilitation is feasible. CIM was associated with less arm impairment at the end of treatment. Long-term studies are needed to determine whether CIM early after stroke is superior to traditional therapies. (Stroke. 2000;31:2984-2988.)

Key Words: cerebrovascular disorders ▪ controlled clinical trials ▪ motor activity ▪ neuronal plasticity ▪ rehabilitation

Stroke has recently been estimated to affect 730 000 persons per year in the United States, with cost estimates ranging from $13 to $30 billion.1 Although most stroke survivors recover to some degree, many survivors are left with significant sensorimotor and cognitive deficits. These deficits produce long-term need for assistance from caregivers and society. Most stroke treatment research has focused on minimizing brain injury in the acute phase, promoting early reperfusion of ischemic brain, developing neuroprotection strategies, and treating cerebral edema.

Another treatment strategy is to promote clinical improvement despite neurological deficit. One potential method to improve sensorimotor recovery after stroke is constraint-induced movement (CIM), or “forced use.”2,3 Most rehabilitation treatments of the hemiplegic patient focus on compensation rather than restoration of upper-extremity (UE) function. Patients are taught to use the unaffected UE for activities of daily living (ADL). In contrast, CIM treatment discourages the use of the unaffected extremity and encourages active use of the hemiplegic arm. The goal is to maximize or restore motor function.

A series of animal studies have shown that the reduced motor activity associated with unilateral deafferentation can be overcome by restraining the unaffected limb to force the animal to use the affected limb. Lesioned animals treated with CIM incorporate these motor gains into functional activities, such as feeding and grooming.3-4 Human studies of CIM treatment in persons with hemiplegia of 6 months’ to decades’ duration2,5-8 report that this treatment improves objective measures of dexterity and motor function.

Taub and colleagues2,3 have suggested that “learned non-use” could account for improvements from CIM. In their model, the patient (or lesioned animal) who has difficulty using the affected side will quickly learn to compensate by using the unaffected side. Because the patient or animal continues to use compensatory strategies, the intrinsic recov-
ery that occurs remains “masked.” Forcing the animal or patient to use the impaired UE reinforces the long-term use of the UE in ADL.3

Recent findings regarding neuroplasticity and cortical reorganization might also explain the reported effectiveness of CIM. Nudo and others9–15 describe cortical representation shrinking after lesioning or sensory/motor deprivation. Changes in representational areas were prevented or reversed by focused motor training in primates with concurrent improvements in motor function.9–15 In addition, functional imaging studies in humans with stroke have found recovery to be associated with shifts of activation during motor tasks involving the affected hand to ipsilateral secondary and tertiary motor areas and to contralateral homologous motor areas.16,17 CIM might be more effective than traditional therapies in promoting these representational changes.16 Finally, the differential effect of CIM could result from superior motor learning in animal subjects—similar to techniques of massed practice or task-specific therapy.19–21

No human studies have compared CIM to traditional UE occupational therapy treatment during the first few weeks after stroke, when rehabilitation is typically delivered. Previous studies involved CIM treatment after standard therapies were completed. We sought to determine, by executing a pilot clinical trial, whether CIM could be implemented during the acute rehabilitation stay (1 to 2 weeks after stroke) and whether CIM is more effective than traditional UE therapies during this time. We hypothesized that hemiplegic stroke patients, treated with CIM rehabilitation within 2 weeks of stroke onset, would show significantly less UE impairment after 14 days of treatment than patients who received traditional rehabilitation treatment.

Subjects and Methods

Design

This was a prospective, randomized, controlled clinical trial, with a blinded observer used to measure the primary end point. The baseline measures were collected after informed consent was obtained. Subjects were individually randomized into experimental or control groups by using a table of random numbers. Study treatment protocols were initiated by rehabilitation day 3. To equalize treatment intensity, the same number of therapy sessions was provided to both groups. When 2 or more study subjects were on the rehabilitation floor at the same time, they were assigned rooms in different hallways and received therapy at different times to prevent unintended crossover. Only persons who completed 14 days of inpatient study treatment were included in the analysis.

Subjects

The Human Studies Committee approved this protocol, and all subjects gave informed consent. Subjects were drawn from the acute stroke and brain injury rehabilitation service, a 32-bed unit admitting more than 250 ischemic stroke survivors yearly. The average inpatient stay is 18 days. The majority of patients are admitted to inpatient rehabilitation within 7 days of stroke onset. Consecutively admitted patients were evaluated for participation in the study. Persons with hemorrhagic stroke were excluded. Screening assessments were administered within 2 days of admission to the rehabilitation floor. Study participants met the following inclusion criteria: (1) admission to inpatient rehabilitation within 14 days of ischemic stroke; (2) persistent hemiparesis leading to impaired UE function, as indicated by a score of 1 or 2 on the motor arm item of the National Institutes of Health Stroke Scale (NIHSS); (3) evidence of preserved cognitive function, as indicated by 0 or 1 on the consciousness, communication, and neglect items of the NIHSS; (4) presence of a protective response, as indicated by scores of ≥3 on the upper-arm item of the Motor Assessment Scale (MAS); and (5) no UE injury or conditions that limited use before the stroke.

Measures

Screening Measures

The NIHSS22,23 was used as a screening tool (see inclusion criteria) and a measure of stroke severity. The upper-arm function item of the MAS was used as a screening tool for inclusion.24 The test measures impairment and disability on a 6-point ordinal scale and includes measures of volitional arm and hand movements, tone, and mobility. For this study, section 2 in the upper-arm function portion was applied. We used this measure to eliminate persons without UE protective reactions.

Primary Outcome Measures

The primary end point for this study was the total Action Research Arm Test (ARA) score after 14 days of treatment. Reliability, construct validity, and predictive validity of the ARA have been well established.25,26 The ARA has been used in other recent clinical trials of motor therapies.8,25,27 The ARA is a functional assessment of UE strength, dexterity, and coordination. Derived from the Fugl-Meyer scale, the ARA includes 19 items divided into 4 subscales: grasp, grip, pinch, and gross movement.26 The performance of each motor task is rated on a 4-point scale, ranging from 0 (no movement possible) to 3 (movement performed normally). Scores on individual items are added, with a maximum score per arm of 57.

Secondary Outcome Measures

The Barthel Index (BI) at discharge from inpatient rehabilitation was used as the measure of basic ADL function.28 The Functional Independence Measure29 (FIM) includes 5 items that specifically assess UE function (eating, grooming, bathing, UE dressing, and lower-extremity dressing). Each item is scored on a 7-point ordinal scale. The BI score, and the score of each of the 5 individual UE ADL items at discharge, were used as secondary end points.

Treatment

Treatment regimens were designed to ensure that patients in both groups received equivalent time and intensity of treatment directly supervised by the occupational therapist. All subjects received routine interdisciplinary stroke rehabilitation, except for the study treatment that occurred during the regularly scheduled occupational therapy sessions. Individualized and circuit-training techniques were used in control and experimental groups. All subjects received study treatment for 2 hours per day, 5 days per week, for 2 consecutive weeks.

Control (Traditional) Occupational Therapy Treatment

The control group received standard occupational therapy treatment that included compensatory techniques for ADL, UE strength and range of motion, and traditional positioning. Subjects also participated in a circuit-training program allowing patients to perform bilateral self-range of motion and functional activities in a supervised setting.

Experimental (CIM) Therapy Treatment

Subjects in the experimental group received a CIM intervention that directed subject attention and effort toward the hemiparetic UE and minimized the use of the uninjured UE during functional activities. To discourage the use of the unaffected hand outside of therapy sessions, subjects wore a padded mitten for at least 6 hours per day during the 14-day treatment period. This method allowed subjects to use the unaffected arm to prevent a fall. Occupational therapy treatment focused on ADLs, UE training which used the affected UE as much as possible. The CIM circuit training encouraged the use of the hemiplegic arm with a variety of UE and functional tasks.
TABLE 1. Baseline Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>CIM (n = 11)</th>
<th>Traditional (n = 9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range 47–83 y)</td>
<td>61.5±13.7</td>
<td>71.4±5.3</td>
<td>0.07</td>
</tr>
<tr>
<td>MMSE, y (range 18–29 y)</td>
<td>26.3±2.5</td>
<td>23.5±4.0</td>
<td>0.20</td>
</tr>
<tr>
<td>NIHSS, y (range 3–37 y)</td>
<td>10.2±9.4</td>
<td>7.5±2.8</td>
<td>0.45</td>
</tr>
<tr>
<td>Impaired side ARA score (range 0–49)</td>
<td>25.9±19.4</td>
<td>27.9±20.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Unimpaired side ARA score (range 53–57)</td>
<td>57.0±0.0</td>
<td>56.4±1.5</td>
<td>0.94</td>
</tr>
<tr>
<td>Right side hemiparesis, %</td>
<td>75</td>
<td>63</td>
<td>0.49</td>
</tr>
<tr>
<td>Women, %</td>
<td>25</td>
<td>63</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Analysis

All data analyses were computed with STATISTICA version 5.1 (Stat-Soft Inc, 1997). Descriptive statistics were computed for each of the variables included in the study. For between-group comparisons of continuous variables, t tests were used. Mann-Whitney U tests and χ² analyses were used when appropriate. ANCOVA was computed to test the study hypothesis.

Results

Of the 23 persons enrolled in the study, 20 completed the 14-day treatment. The characteristics of the remaining study participants are shown in Table 1. Mean time to randomization was 6±2.6 days (range 4 to 14 days). The mean age of the traditional group was almost 10 years greater than that of the subjects in the CIM group, but this difference was not statistically significant (t = −1.92, P < 0.07). There were no significant differences between the groups for lesion location (left versus right), Mini-Mental State Examination scores, or NIHSS scores. The gender distributions were unequal between the groups (there were more men in the CIM group); however, this difference was not statistically significant (χ² = 1.65, P < 0.19).

As expected, total ARA scores for the unimpaired extremities were normal for both groups at each time of testing. All posttreatment assessments were performed by blinded testers on study day 15. The pretest and posttest ARA scores are presented in Table 2. The pretest total ARA score was used as a covariate, and ANCOVA was computed for the posttest total ARA scores. After the 14 days of treatment, the mean total ARA score was significantly higher in patients who received CIM treatment than in patients in the traditional treatment group (F₁₁₁ = 11.70, P < 0.003). Thus, the study hypothesis was supported; effect size was r = 0.66.

The posttest grip, pinch, grasp, and gross motor scores for each group were compared by using Mann-Whitney U tests. These findings are presented in Table 2. All mean posttreatment ARA subtest scores were higher for patients in the CIM group; only the pinch subtest scores achieved statistical significance (U = 13.50, P < 0.03). BI and FIM scores at discharge were used as secondary end points for the study. The BI and FIM item scores are presented in Table 3. There were no significant differences in BI scores at discharge (t = 1.14, P < 0.27). The 5 FIM UE item scores at discharge were also compared. On each item, the mean scores were higher for the CIM group. The only significant difference occurred on the UE dressing item (t = 2.16, P < 0.04).

Discussion

CIM, or “forced-use,” treatment may be an appropriate method to improve sensorimotor recovery after stroke. Most rehabilitation treatments for hemiplegic patients focus on compensatory strategies to promote independence in ADL by any means rather than restoration of UE function. Typically, patients are taught to use the unaffected UE and various assistive devices for ADL. In contrast, CIM treatment discourages the use of the unaffected UE and encourages the use of the hemiplegic arm. The goal of this treatment is to maximize or restore motor function. Before the present study, no studies had tested this treatment in the acute phase of stroke recovery during inpatient stroke rehabilitation.

This pilot study demonstrates that a clinical trial of CIM therapy during acute rehabilitation is feasible. We found a statistically significant improvement in our primary end point, the total ARA score, at the end of 14 days of treatment compared with the standard occupational therapy treatment. All subjects tolerated the treatment, and there was no evidence of excess disability associated with CIM treatment. We emphasize that both groups received the same amount of time with the occupational therapy staff, and so the CIM treatment did not involve more therapy resources than routinely used in our unit.

This pilot trial involved a relatively small number of subjects and did not address the persistence of any treatment effect. Although there was no statistically significant difference in age between the 2 treatment groups, the trend toward younger age in the CIM group could have affected the results of this study. Caution must be used in making any statements about the effectiveness of CIM in the acute rehabilitation setting. We found statistically significant differences using the prespecified end point of the total ARA score. While this
result is subject to all the vagaries of a small trial, there was nonetheless a moderate-to-large effect size ($r=0.66$) for this treatment. Other analyses of the data also support this finding. The CIM group had higher scores on all the ARA subscales, though only the pinch scale achieved statistical significance. There was no difference in overall disability as measured by the BI. However, the CIM group had higher scores on the 5 FIM items that require the use of the arms.

Several safety concerns have been postulated regarding CIM treatment in the acute rehabilitation setting. Painful overuse syndromes and the frustration of focusing on a weak and clumsy limb have been raised as potential problems. No subjects withdrew from the study, suggesting that overuse and frustration are not obstacles to the use of this treatment during acute rehabilitation. Another concern about early use of CIM is that the emphasis on motor restoration might compromise compensatory techniques and thus lead to excess disability. Our study found no suggestion that patients who received CIM were less independent in ADL at the end of the treatment period.

Another safety concern arises from animal studies showing that very intense motor activity, early after lesion, increased stroke lesion volume. Lesion enlargement has been reported in rats placed in conditions that force immediate and extreme overuse of the affected forelimb. This lesion enlargement has been attributed to excitotoxicity or exercise-induced hyperthermia. On the other hand, enriched environments that encourage motor activity improved outcome without increasing lesion volume in rodents. Our study tested treatment intensities that were much lower than those used in the animal studies, and all subjects received the routine amounts of therapy delivered in our clinical service. Our subjects were neurologically stable when study treatments were initiated.

The relevance of the animal data to the clinical rehabilitation setting is unknown, but our results are reassuring. The relative improvement in the CIM group does not directly address the question of activity-dependent lesion enlargement in humans. However, even if such enlargement were to occur, the improvements in motor outcomes seen in this trial would call into question the biological significance of any enlargement.

The “best” primary end point for a UE motor intervention has not been established. Even after dozens of acute stroke trials, no single measure is widely accepted as the “best” end point for hyperacute stroke intervention trials. Most disability measures do not distinguish unilateral from bilateral accomplishment of ADL tasks and would be insensitive to the expected results of a UE motor intervention trial. Other studies have used subject self-reports; we did not choose this method because of the uncertain validity of such reports in the rehabilitation setting and because self-report would circumvent the blinding process. The ultimate goal of treatment is to maximize social participation and quality of life. However, in the early phase of treatment development, it seemed most reasonable to use measures that directly assessed the mechanism by which gains in social participation and quality of life would be achieved.

Several lines of reasoning support early implementation of CIM. From a motor learning perspective, early implementation might minimize learned nonuse. It might be easier to prevent behaviors than attempt to extinguish them once they are established. Primate data also suggest that early implementation of motor training could prevent shrinkage of cortical representational areas. There might also be a window of opportunity after brain injury. Rodent studies suggest a defined period after injury during which synaptic arborization and pruning occur. Although preliminary, our findings suggest that CIM, during acute stroke rehabilitation, could improve motor function without increasing treatment time. Previous CIM studies included persons with chronic hemiplegia, typically 6 months to many years after stroke onset. Chronic CIM trials represent an added period of treatment that requires new resources for implementation.

This investigation demonstrates that a randomized controlled trial of this nonpharmacologic stroke therapy is feasible even under the clinical conditions currently found in the United States. The results of our study are promising enough to justify further clinical studies. A larger sample size and community follow-up would allow the definitive determination of whether early CIM provides long-term and clinically significant benefits versus traditional UE therapies.

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**References**


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