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Early and Repetitive Stimulation of the Arm Can Substantially Improve the Long-Term Outcome After Stroke: A 5-Year Follow-up Study of a Randomized Trial

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Background and Purpose—Several studies have investigated the effect of therapeutic interventions for the arm in the acute phase after stroke, with follow-ups at a maximum of 12 months. The aim of this study was to examine the effect of repetitive sensorimotor training of the arm at 5 years after stroke.

Subjects and Methods—One hundred consecutive stroke patients were randomly allocated either to an experimental group that received daily additional sensorimotor stimulation of the arm or to a control group. The intervention period was 6 weeks. Assessments of the patients were made before, midway, and after intervention, and at 6 and 12 months after stroke. In this study, 62 patients were reassessed at 5 years after stroke. The Brunnström-Fugl-Meyer (BFM) test, Action Research Arm (ARA) test, and Barthel index (BI) were used as the primary outcome measures.

Results—At the 5-year follow-up, there was a statistically significant difference for both the BFM and ARA tests in favor of the experimental group. The mean differences in improvement between the groups from the initial evaluation to the 5-year assessment corresponded to 17 points on the BFM and 17.4 on the ARA. No effect was found for the BI. The treatment was most effective in patients with a severe initial motor deficit.

Conclusions—Adding a specific intervention for the arm during the acute phase after a stroke resulted in a clinically meaningful and long-lasting effect on motor function. The effect can be attributed to early, repetitive, and targeted stimulation. (Stroke. 2004;35:924-929.)

Key Words: stroke ■ rehabilitation ■ clinical trial

Numerous articles have been published in which the effects of various treatment methods for improving arm function have been evaluated.1 In many studies, therapeutic interventions were applied to chronic stroke patients; however, the emphasis on rehabilitation efforts is concentrated in the acute phase after stroke.

Three major randomized controlled trials2–4 have evaluated the effect of more intensive therapy. Sunderland et al2 found a statistically significant improved motor and functional recovery after a more intensive treatment regime. This advantage diminished to a non-significant trend by 1 year.3 In a study by Kwakkel et al,3 a higher intensity of upper limb function training resulted in small improvements in dexterity after treatment. No significant gains could be shown at follow-up assessments 9 and 12 months after stroke.6 Lincoln et al4 could not show a difference between patients who received additional therapy for the arm and routine therapy, but a subanalysis of the same data7 revealed statistically significant benefits for the less severely impaired patients that were sustained at the 6-month follow-up assessment. These 3 studies indicate that a more intensive rehabilitation program is beneficial, but there is no evidence of a sustained effect.

Several studies have investigated the effect of targeted interventions in the acute phase such as EMG biofeedback,8 repetitive motor training of hand and fingers,9,10 active neuromuscular stimulation for the wrist and fingers,11,12 sensorimotor stimulation of the arm,13 and robot-delivered sensorimotor training.14 The results of the studies mentioned indicate that additional focused therapy for the arm leads to an improved motor outcome immediately after the intervention. In 3 of the 7 studies,9,10,14 no follow-up evaluation was performed.
performed. Results at follow-up assessments in the other studies\textsuperscript{8,11–13} were divergent.

To the best of our knowledge, the effects of treatment interventions have not been evaluated on a long-term basis. The objective of the present study was to examine the effect of a repetitive sensorimotor training of the arm on the outcome at 5 years after stroke. The results in the first year after stroke have been published in a previous article.\textsuperscript{13}

Subjects and Methods

Subjects and Design

From March 1994 until September 1996, patients were recruited from 4 rehabilitation centers. The criteria for inclusion in the trial were: (1) a diagnosis of ischemic brain damage or intracerebral hemorrhage; (2) an obvious motor deficit of the upper limb (Brunnstrom-Fugl-Meyer\textsuperscript{14} [BFM] score <46); and (3) the ability to perform the experimental treatment independently. Patients were excluded if they had had a previous stroke on the same side or a pre-stroke disability affecting the arm function. Patients were admitted to the trial between 2 and 5 weeks after the onset of stroke. A single-blind, stratified, randomized, controlled design was used. Patients were stratified according to their initial motor score on the BFM test\textsuperscript{15} and the type of stroke. The number of patients was calculated a priori to ensure sufficient statistical power. Detailed information on the subjects and study design has been reported in a previous article.\textsuperscript{13}

The procedures followed were in accordance with the ethical standards of each hospital’s institutional committees on human experimentation. Informed consent was obtained from all patients participating in the study.

Treatment Conditions

In the experimental group the patients were positioned in a rocking chair. The arm was supported by an inflatable long-arm splint in a position contrary to the typical pattern of spasticity and the hand was fixed in a gutter. The patients were asked to perform rocking movements, pushing with the hemiplegic arm. The chair was balanced in such a way that during the rocking movements, patients fell slightly forward and had to actively push backward. This experimental intervention emphasized motor stimulation through the repeated movements facilitating muscle activity and sensory stimulation. The treatment modality originates from Johnstone.\textsuperscript{16} The patients in the control group were also positioned in a rocking chair. They received fake short-wave therapy of the shoulder during rocking.

In both groups, the intervention was performed on a daily basis during a period of 6 weeks. Each treatment session lasted 30 minutes. All patients received the full 30 sessions of treatment. The intervention was performed in addition to the usual rehabilitation procedures and was performed by the same therapists for patients in the control and experimental groups.

Evaluation

Subjects were re-assessed at 5 years after onset of stroke for the same primary outcome measures used during the first year of the study (before, midway, and after the intervention period, and during a follow-up at 6 and 12 months), including the subscale of the upper limb of the BFM test, the Action Research Arm (ARA) test, and the Barthel index (BI). All scales meet the criteria of reliability and validity and have been described in a previous article.\textsuperscript{13} A single assessor, who was blind to the patients’ allocation to either the experimental or the control group, performed all assessments at the 5-year mark.

Additional parameters such as hemianopia, hemi-inattention, sensory function, and muscle tone (Ashworth scale) were assessed at the initial evaluation\textsuperscript{13} to investigate whether certain patients would benefit more from the experimental intervention than others.

Data Analysis

The characteristics of the dropouts from the control and experimental groups were compared using unpaired $t$ tests or $\chi^2$ tests. To further investigate if dropout was related to the primary outcome measures, a logistic regression analysis was performed using the BFM, ARA, and BI at baseline and at 1 year as independent variables. Age was used as a confounding variable.

Patient characteristics of the experimental and control groups in the 5-year follow-up study were compared using unpaired $t$ tests, $\chi^2$, or Fisher exact tests. Wilcoxon rank sum tests were applied to assess the differences for the BFM, ARA, and BI between the control and the experimental groups at baseline and the 1- and 5-year follow-ups. The differences for changes from baseline to 5 years and from 1 year to 5 years showed a normal distribution. Therefore, unpaired $t$ tests were used to evaluate the differences for change. Additionally, Cohen $d$ effect size was calculated.\textsuperscript{17} According to Cohen,\textsuperscript{17} effect sizes of 0.2 to 0.5 are considered as small, 0.5 to 0.8 are medium, and >0.8 are large.

Patients were subdivided into 3 categories—improved, stable, and deteriorated—based on the pattern of recovery between baseline and 5 years. The criteria for improvement or deterioration were based on a study by Van der Lee et al.\textsuperscript{18} This study indicated that a difference of 10% on the BFM ($\pm 6.6$) and ARA ($\pm 5.7$) corresponded with the limits of agreement during test–retest.

To identify subgroups of patients who would benefit most from this type of treatment, a multivariate ANOVA for repeated measures was applied for the logarithmic scores on the BFM using several prognostic factors, the treatment group, and the interactions of the prognostic factors and treatment group as independent variables. A significant interaction indicates a differential treatment effect. Prognostic factors included the degree of motor deficit, level of muscle tone, sensory loss, and hemianopia or hemi-inattention. This analysis was not performed for the ARA because the data could not be transformed to normality.

All statistical procedures were performed with the SAS System. In hypothesis testing, 0.05 was used as the level of significance.

Results

Subjects

One hundred patients participated in the study. The progress made during the trial is shown in Figure 1. At the 5-year follow-up, 62 patients were re-assessed. Death, refusal to participate further, recurrent stroke, and poor medical condition accounted for the missing scores. In logistic regression analysis, age was found to be a significant predictor of dropout ($P=0.0002$). This indicates that patients with an older age had a greater chance to dropout. Corrected for age, the BFM, ARA, and BI at baseline and 1 year were not significantly related to the occurrence of dropout. Also the number of dropouts was not significantly different between both groups ($P=0.41$). Age ($P=0.42$), sex ($P=0.49$), and side of paresis ($P=0.51$) were similar in the dropouts from the control and the experimental group. Statistical analysis of the 3 primary outcome parameters (BFM, ARA, BI) on the remaining 62 patients during the first year showed identical results as reported in the previous study on 100 patients.\textsuperscript{13} This is illustrated in Figure 2 for the BFM. Previous findings indicate no relationship between the primary outcome measures and the dropout process. Therefore, further results were based on a complete case analysis of the 5-year follow-up group of 62 subjects.

Patient details for the control and experimental groups at the 5-year follow-up are shown in Table 1. The groups were comparable except for type of lesion.
Efficacy of the Therapeutic Intervention

Table 2 shows the results of the BFM, ARA, and BI for the control and experimental groups at baseline and 5 years after onset of stroke. No significant differences were found at baseline. At the 5-year follow-up, there was a statistically significant difference for the BFM and ARA in favor of the experimental group. This group improved on average by 28.5 points (CI: 22.1 to 34.9) on the BFM, whereas the control group improved by 11.5 points (CI: 6.0 to 16.9). This implies a difference in improvement of 17 points between groups (CI: 8.7 to 25.4; P<0.0001). The mean improvement in the control group and the experimental group on the ARA was 12.1 (CI: 5.2 to 19.1) and 29.5 (CI: 21.7 to 37.2), respectively. The mean difference in improvement was 17.4 (CI: 7.0 to 27.7).

**TABLE 1. Baseline Characteristics of the Control and Experimental Group**

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Experimental Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X (SD)</td>
<td>58.14 (10.86)</td>
<td>62.34 (11.33)</td>
<td>0.14 (t)</td>
</tr>
<tr>
<td>Range</td>
<td>36–77</td>
<td>38–81</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>24</td>
<td>0.24 (x)</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Side of paresis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>16</td>
<td>15</td>
<td>0.45 (x)</td>
</tr>
<tr>
<td>Right</td>
<td>13</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia</td>
<td>24</td>
<td>33</td>
<td>0.02 (Fisher)*</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* F indicates f-test; x, chi-square test; Fisher, Fisher exact test.

*P<0.05
The effect sizes for the BFM and ARA between baseline and 5 years were 1.04 and 0.83, respectively. The mean difference between 1 year and 5 years on the BFM was 3.9 (CI: 7.9 to 0.2; \( P = 0.06 \)) in the control group and 2.7 (CI: 0.6 to 6.0; \( P = 0.11 \)) in the experimental group. For the ARA, the mean difference was 4 (CI: 8.7 to 0.67; \( P = 0.09 \)) and 7.18 (CI: 3.3 to 11.0; \( P = 0.0006 \)) in the control and experimental group, respectively. The mean difference between the changes in scores from 1 year to 5 years between control and experimental group was 6.6 (CI: 1.5 to 11.7; \( P = 0.01 \)) for the BFM and 11.2 (CI: 5.3 to 17.0; \( P = 0.0003 \)) for the ARA. There were no significant differences for the BI for all comparisons.

Figure 3 shows the distribution of the patients into 3 categories (deteriorated, improved, stable) based on the changes in scores between baseline and 5 years. For the BFM, 55% of patients improved in the control group versus 90.9% in the experimental group. For the ARA, this was 44.8% and 75.8%, respectively.

Figure 4. Mean and standard errors of the logarithmic scores on the Brunnström-Fugl-Meyer test preceding, midway, and after the intervention period, and at follow-up at 6 months, 12 months, and 5 years in the 2 subgroups of patients of the control and experimental groups with an initial severe (A) or moderate (B) motor deficit.

The multivariate ANOVA for repeated measures on the logarithmic scores of the BFM revealed no significant interactions for the investigated factors of muscle tone (\( P = 0.15 \)), sensory loss (\( P = 0.20 \)), hemianopia and/or hemi-inattention (\( P = 0.93 \)). A significant interaction was found between the treatment group and motor deficit (\( P = 0.05 \)). The differences in recovery on the BFM test between the control group and the experimental group were larger for patients with a severe initial motor deficit as compared with the moderately impaired patients (Figure 4).

Discussion

This study investigated the long-term effect on the motor and functional recovery of the arm resulting from an additional therapeutic intervention in the acute phase. The pattern of recovery of the patients who could be followed-up over the
full 5 years was consistent with the group assessed during the first year. Further data exploration suggested that our complete case analyses are likely to provide valid statistical interferences. A multivariate ANOVA model for repeated measures, taking into account all measurements for all patients, revealed a significant group by time interaction effect for the BFM (P = 0.003) and no significant effect for the BI. Post-hoc comparisons for the BFM revealed a significant difference between groups at 5 years (P = 0.008). These results are valid under less strict assumptions about the relation between dropout and outcome than our earlier complete case results. For the ARA, data could not be transformed to normality; therefore, this statistical model could not be used. For reasons of homogeneity of analysis for all primary outcome measures, results of complete case analysis were reported.

In the intervention studies of arm function using a 6- to 12-month follow-up, significant treatment effects disappeared over time. The results of this study showed that additional repetitive sensorimotor stimulation in the acute phase significantly improved motor and functional recovery 5 years after stroke. Large effect sizes (> 0.8) were found for both motor control (BFM) and functional ability (ARA). No effect was found on the BI. This is not surprising because the BI is an overall index of functional recovery, and the functions related to the upper limb may be compensated with the non-hemiplegic arm.

Differences between the control and experimental group at follow-up seemed to be the result of a continued improvement between 1 year and 5 years in the experimental group (BFM: nonsignificant trend; ARA: significant improvement) combined with a nonsignificant trend of decrease of function in the control group. The late effect on functional recovery (ARA) might be explained by the nature of the therapy. The intervention consisted of repetitive stimulation of muscle activity. Therefore, the acquired basic movements may have provided a basis for the training of further activities during the follow-up period. In such a long-term follow-up in which dropout is inevitable, there is also a probability that the results may be influenced by factors (known and unknown) that contribute to survival rather than to the intervention. However, because of the randomization, we expect these factors to be similar in control and experimental group. Several findings in the remaining 62 patients of 5-year follow-up group further indicated that the experimental and control group had similar expectations toward recovery. Patient characteristics were similar in both groups, with exception of the type of stroke. The 5 subjects who had an intracerebral hemorrhage all belonged to the control group. However, the type of stroke was not found to be a significant predictor of motor recovery of the arm. Also, both groups had similar scores on the BFM, ARA, and BI at the start of the study. It has been shown that the initial motor deficit is the most important prognostic factor for arm function recovery.

Approximately 30% more patients in the experimental group showed an improvement on the BFM and ARA, beyond the minimal clinical important difference, than in the control group between baseline and 5 years. This indicates that the therapeutic intervention improved arm function for a substantial number of stroke patients. The intervention was most effective for the select group of severely affected patients. These results are remarkable because in other studies, favorable results were mainly found in patients with moderate motor deficit. For patients with a severely paralyzed arm, this therapy may have created a structured environment in which they could practice repetitive movements of the arm. The importance of the repetitive element in therapy is endorsed by other studies. The learning environment of the intervention was limited. There was virtually no variation in the task and the input was not meaningful. This may explain why the therapy was not effective for the less severely affected patients. The results of this study are in agreement with the basic rules of motor (re)learning.

The recent findings on adaptive plasticity in the recovery of function after damage to the motor cortex may support the effectiveness of the intervention. Retraining of skilled hand use in primate studies has resulted in prevention of the loss of hand territory adjacent to the infarct and has shaped subsequent functional reorganization in the undamaged surrounding motor cortex. Human studies using functional imaging techniques also have demonstrated a complex pattern of cortical reorganisation after recovery from stroke. It could be speculated that the increased afferent input of the arm in our study prevented shrinking of the cortical representation of arm and hand and modulated neuroanatomic and neurophysiologic changes in the undamaged tissue. The question of whether rehabilitation can adaptively modulate the plasticity process that inevitably occurs after cortical injury will be a challenging issue for future studies.

To accomplish the desired rewiring of brain activity and cortical re-mapping, an appropriate and high dose of afferent input in the right context seems to be of paramount importance. The amount of stimuli that professionals can give to patients is next to nothing in comparison with normal daily activities. Strategies need to be developed whereby patients can take responsibility for their own therapy. Beneficial results have been reported after constraint-induced movement therapy, a method that forces patients to use the affected arm by means of immobilization of the unaffected arm in combination with intensive training of the paretic arm. This method is mainly applicable in patients with moderately affected arm function. In the intervention in our study, patients were forced to move the arm autonomously for half an hour per day during 30 sessions over a period of 6 weeks. This resulted in 15 hours of additional focused therapy in the acute phase. This is a time period in which nearly no autonomous active treatment alternatives for the arm are available. This method may be an alternative for augmenting the afferent input for severely affected arms of patients in the early stages after stroke onset.

In conclusion, early and repetitive stimulation of the arm resulted in a clinically important long-lasting effect. Stroke patients should be encouraged to intensively exercise their affected arm. Studies suggest that interventions should be intensive, repetitive, and targeted.
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