Dose–Response Relationship of Robot-Assisted Stroke Motor Rehabilitation
The Impact of Initial Motor Status

Yu-wei Hsieh, PhD; Ching-yi Wu, ScD; Keh-chung Lin, ScD; Grace Yao, PhD; Kuen-yuh Wu, PhD; Ya-ju Chang, PhD

Background and Purpose—The increasing availability of robot-assisted therapy (RT), which provides quantifiable, reproducible, interactive, and intensive practice, holds promise for stroke rehabilitation, but data on its dose–response relation are scanty. This study used 2 different intensities of RT to examine the treatment effects of RT and the effect on outcomes of the severity of initial motor deficits.

Methods—Fifty-four patients with stroke were randomized to a 4-week intervention of higher-intensity RT, lower-intensity RT, or control treatment. The primary outcome, the Fugl-Meyer Assessment, was administered at baseline, midterm, and posttreatment. Secondary outcomes included the Medical Research Council scale, the Motor Activity Log, and the physical domains of the Stroke Impact Scale.

Results—The higher-intensity RT group showed significantly greater improvements on the Fugl-Meyer Assessment than the lower-intensity RT and control treatment groups at midterm (P=0.003 and P=0.02) and at posttreatment (P=0.04 and P=0.02). Within-group gains on the secondary outcomes were significant, but the differences among the 3 groups did not reach significance. Recovery rates of the higher-intensity RT group were higher than those of the lower-intensity RT group, particularly on the Fugl-Meyer Assessment. Scatterplots with curve fitting showed that patients with moderate motor deficits gained more improvements than those with severe or mild deficits after the higher-intensity RT.

Conclusions—This study demonstrated the higher treatment intensity provided by RT was associated with better motor outcome for patients with stroke, which may shape further stroke rehabilitation.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00917605.

Key Words: randomized controlled trial ■ robot-aided neurorehabilitation ■ stroke ■ treatment dosage

Stroke remains a common cause of acquired adult disability worldwide.1,2 Motor deficits of the upper limb are often a devastating disability for stroke survivors3 and thus, the search for effective and efficient rehabilitation to promote motor recovery becomes urgent. Robot-assisted therapy (RT) is an innovative approach to stroke rehabilitation that uses intensive, repetitive, interactive, and individualized practice as an optimal strategy to enhance motor learning.4,5

The optimal dosage for specific rehabilitation regimens to induce improvement is unclear from current evidence.6 Because the research suggests that intensive therapy has a positive influence on stroke recovery,7,8 RT may offer a good way to close the gap between limited rehabilitation resources and a greater amount of therapy.9 RT also provides precise and quantifiable control of therapy, allowing better research into treatment dosage.10 This critical factor—how the intensity of therapy influences the effects of RT—should be addressed to inform the dose–response relation and to seek proper treatment intensity for patients.

Another emerging concern is which intervention is most beneficial for which type of patient under specific circumstances.11 Identifying the factors affecting successful outcomes and the patients most likely to respond to the therapy would be informative for clinical guidelines. Although the initial motor status of patients with stroke is viewed as an important factor that influences recovery,12,13 whether this factor affects the outcomes of RT remains unknown. We therefore investigated the effects of RT on clinical outcomes in patients with chronic stroke by using higher-intensity and lower-intensity RT relative to a duration-matched control...
treatment (CT) and also examined whether the initial severity of motor deficits and the treatment intensities of RT interact to influence the primary outcome.

Methods

Participants
Criteria for study participants were (1) more than 6 months’ onset from a unilateral stroke; (2) baseline upper extremity score on the Fugl-Meyer Assessment (FMA) of 26 to 56; (3) no excessive spasticity in forearm and wrist joints (modified Ashworth scale <3); (4) able to follow study instructions and perform study tasks (Mini-Mental Status Examination ≥22); (5) no upper limb fracture within 3 months or painful arthritis of the joints; and (6) no severe neuropsychologic impairments (eg, global aphasia or severe attention deficits). The Institutional Review Boards of the participating hospitals approved the study, and all participants provided informed consent.

Study Procedures
This was a randomized-block controlled trial with pretest, midterm, and posttest evaluations. Eligible participants were stratified according to side of lesion and level of motor deficits and individually randomized to receive one of the 3 interventions. A random number table was used to generate randomization assignments, and a research assistant allocated the patients to an intervention group accordingly. All clinical measures were administered to the patients at baseline and immediately after the intervention by the same blinded rater. The primary outcome measure was also administered 2 weeks after treatment began (midterm).

Interventions
All participants received a duration-matched intervention for 90 to 105 minutes/day, 5 days/week for 4 weeks. The patients in the 2 RT groups practiced with the Bi-Manu-Track (Reha-Stim Co, Berlin, Germany; Figure 1), which allows 2 movement patterns: forearm pronation–supination and wrist flexion–extension. Each movement pattern is enabled by 3 computer-controlled modes: passive–passive (mode 1), active–passive (mode 2), and active–active mode (mode 3). The parameters of movement and resistance can be adjusted individually. The robot was equipped with a computer game to provide instant visual movement feedback and to increase participation.

Within one training session, the patients in the higher-intensity RT group practiced 600 to 800 repetitions of modes 1 and 2 for 15 to 20 minutes and 150 to 200 repetitions of mode 3 for 3 to 5 minutes for bilateral forearm and wrist movements. One repetition indicated one movement direction. Patients in the higher-intensity RT received
twice the number of the repetitions per unit of time than patients in the lower-intensity RT group.15

Before the RT training, 5 minutes of mobilization warm-up were provided. After the training, the patients received 15 to 20 minutes of functional activities practice to help them transfer the acquired motor ability to their performance of daily activities.

The CT group received an intensive therapist-administered control therapy matched in duration with the RT groups. Occupational therapy techniques used in the treatment protocols included neurodevelopmental treatment, muscle strengthening, fine-motor training, and functional task training.

Outcome Measures
The primary outcome was a change in the FMA. The 33 upper extremity items of the FMA, with scores ranging from 0 to 66, were used to assess motor impairment.16 The reliability, validity, and responsiveness of the FMA in patients with stroke have been well established.16–18

Secondary outcomes included the following assessments: (1) the Medical Research Council scale, a reliable measurement ranging from 0 (no contraction) to 5 (normal power), examines muscle power of the affected arm;16 (2) the Motor Activity Log consists of a 30-question interview in which patients rate the amount of use and quality of movements at the time of using their affected arm to accomplish daily activities;18 and (3) the Stroke Impact Scale (SIS) 3.0 has 4 physical domains—strength, activities of daily living/instrumental activities of daily living, mobility, and hand function—that use patient report to evaluate function and quality of life.21

Two common complications after stroke, pain and fatigue,22 were measured to investigate if intensive rehabilitation causes adverse effects. The therapist asked the patient to rate the severity of his or her pain and fatigue during the intervention on a scale of 0 (no pain and no fatigue) to 10 (unbearable pain and exhaustion).

Statistical Analysis
An intention-to-treat analysis was applied. Two-way repeated-measures analysis of covariance was used to evaluate efficacy of the primary outcome among the 3 groups followed by a post hoc analysis using the Bonferroni test for a significant effect. Analysis of covariance was used to evaluate treatment efficacy for the secondary outcomes with baseline scores as the covariates. The t test was used to examine recovery rates of each week on each outcome (ie, improved score divided by the number of weeks) between the 2 RT groups. We also examined whether the initial severity of motor impairments affected the primary outcome (ie, FMA). Scatterplots with quadratic curves were used to illustrate the relationship between the baseline scores and the change scores.

Results
The study enrolled 54 patients. One patient in the CT group dropped out due to a medical problem unrelated to the study treatment (Figure 2). The 3 groups did not differ significantly in baseline characteristics (P=0.40–0.93; Table 1). As determined by the obtained effect size of the primary outcome, post hoc power was calculated to be 0.80.

Primary Outcome
On the FMA total score, there was a significant group×time interaction effect (F3,4,93.38=3.95, P=0.01). All 3 groups showed significant within-group gains on the FMA total score from baseline to midterm and from baseline to posttreatment (all P<0.05; Table 2). Analysis of covariance revealed significant differences among the 3 groups at midterm (F2,50=6.97, P=0.002) and at posttreatment (F2,50=4.80, P=0.01). Post hoc analyses showed that the higher-intensity RT group had significantly greater improvements on the FMA total score than the lower-intensity RT and CT groups at midterm (P=0.003 and P=0.02; respectively; Table 2). No significant differences were found between the lower-intensity RT and CT groups at midterm and at posttreatment.

A similar effect was also found on the FMA distal score and no fatigue) to 10 (unbearable pain and exhaustion).

Statistical Analysis
An intention-to-treat analysis was applied. Two-way repeated-measures analysis of covariance was used to evaluate efficacy of the primary outcome among the 3 groups followed by a post hoc analysis using the Bonferroni test for a significant effect. Analysis of covariance was used to evaluate treatment efficacy for the secondary outcomes with baseline scores as the covariates. The t test was used to examine recovery rates of each week on each outcome (ie, improved score divided by the number of weeks) between the 2 RT groups. We also examined whether the initial severity of motor impairments affected the primary outcome (ie, FMA). Scatterplots with quadratic curves were used to illustrate the relationship between the baseline scores and the change scores.

Results
The study enrolled 54 patients. One patient in the CT group dropped out due to a medical problem unrelated to the study treatment (Figure 2). The 3 groups did not differ significantly in baseline characteristics (P=0.40–0.93; Table 1). As determined by the obtained effect size of the primary outcome, post hoc power was calculated to be 0.80.

Primary Outcome
On the FMA total score, there was a significant group×time interaction effect (F3,4,93.38=3.95, P=0.01). All 3 groups showed significant within-group gains on the FMA total score from baseline to midterm and from baseline to posttreatment (all P<0.05; Table 2). Analysis of covariance revealed significant differences among the 3 groups at midterm (F2,50=6.97, P=0.002) and at posttreatment (F2,50=4.80, P=0.01). Post hoc analyses showed that the higher-intensity RT group had significantly greater improvements on the FMA total score than the lower-intensity RT and

| Table 1. Baseline Characteristics of the Study Participants by Group (N=54) |
|-----------------------------|-----------------------------|-----------------------------|
| Characteristics*            | Higher-Intensity RT (n=18)  | Lower-Intensity RT (n=18)   | Control Treatment (n=18) | P Value |
| Age, y                      | 56.51 (10.03)               | 52.21 (12.20)               | 54.83 (9.84)              | 0.49    |
| Time after stroke, mo       | 28.67 (13.67)               | 23.28 (15.37)               | 22.44 (15.34)             | 0.40    |
| Sex, no.                    | 11                          | 13                          | 12                         | 0.78    |
| Male                        | 7                           | 5                           | 6                          |         |
| Female                      |                             |                             |                            |         |
| Stroke subtype, no.         | Ischemic                    | 12                          | 11                         | 9       | 0.73    |
|                             | Hemorrhagic                 | 6                           | 7                          | 8       |         |
|                             | Subarachnoid                | 0                           | 0                          | 1       |         |
| Side of stroke, no.         | Right                       | 9                           | 9                          | 8       | 0.93    |
|                             | Left                        | 9                           | 9                          | 10      |         |
| MMSE score                  | 28.50 (1.98)                | 28.00 (2.50)                | 28.28 (2.08)               | 0.79    |
| FMA score                   | 42.78 (8.86)                | 43.11 (9.18)                | 44.61 (11.06)              | 0.84    |

CT groups at midterm (P=0.003 and P=0.02) and at posttreatment (P=0.04 and P=0.02; respectively; Table 2). No significant differences were found between the lower-intensity RT and CT groups at midterm and at posttreatment. A similar effect was also found on the FMA distal score (Table 2).

Table 2. Descriptive Statistics and Group Comparisons on the Primary Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Higher-Intensity RT Mean (SD)</th>
<th>Lower-Intensity RT Mean (SD)</th>
<th>Control Treatment Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMA total score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>42.78 (8.86)</td>
<td>43.11 (9.18)</td>
<td>44.61 (11.06)</td>
</tr>
<tr>
<td>Midterm</td>
<td>46.02 (6.50)†</td>
<td>44.50 (9.69)*</td>
<td>46.33 (10.50)*</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>48.00 (8.22)†</td>
<td>46.33 (10.27)*</td>
<td>47.56 (10.50)*</td>
</tr>
<tr>
<td>FMA distal score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.56 (6.17)</td>
<td>11.44 (6.81)</td>
<td>13.39 (7.65)</td>
</tr>
<tr>
<td>Midterm</td>
<td>14.00 (5.99)*</td>
<td>12.22 (7.14)*</td>
<td>14.06 (7.67)*</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>15.17 (5.93)*</td>
<td>13.06 (7.53)*</td>
<td>14.72 (7.51)*</td>
</tr>
<tr>
<td>FMA proximal score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>30.22 (4.01)</td>
<td>31.67 (3.96)</td>
<td>31.22 (4.60)</td>
</tr>
<tr>
<td>Midterm</td>
<td>32.06 (3.76)†</td>
<td>32.28 (4.17)†</td>
<td>32.28 (4.07)*</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>32.83 (3.62)†</td>
<td>33.28 (3.72)*†</td>
<td>32.83 (4.25)*†</td>
</tr>
</tbody>
</table>

RT indicates robot-assisted therapy; FMA, Fugl-Meyer Assessment.

*Continuous data are presented as the mean (SD); categoric data are presented as indicated.
Secondary Outcomes and Adverse Responses
The 3 groups made significant within-group improvements over time (all \(P<0.05\) on the Medical Research Council and Motor Activity Log; however, the improvements were not significantly different among the 3 groups on the Medical Research Council \((F_{2,50}=1.41, P=0.25)\), the Motor Activity Log quality of movements \((F_{2,50}=2.38, P=0.10)\), or the Motor Activity Log amount of use \((F_{2,50}=1.61, P=0.21)\). The higher-intensity RT group reported significant within-group improvements on the SIS–strength \((P=0.002)\) and SIS – activities of daily living/instrumental activities of daily living \((P=0.02)\) assessments. The lower-intensity RT group had significant within-group improvements on the SIS–strength assessment \((P=0.02)\). The CT group, however, did not report significant improvements on the 4 SIS physical domains \((P=0.07–0.29)\). The between-group comparison did not show a significant difference among the 3 groups for \(P=0.02\)–0.86; Table 3); however, the recovery rate values for the higher-intensity RT group were generally higher than those for the lower-intensity RT group.

Recovery Rates
Recovery rates of the higher-intensity RT group on the FMA total and distal scores were significantly higher than those of the lower-intensity RT group at midterm and posttreatment \((P=0.05\); Table 3). On the secondary outcomes, differences in recovery rates between the 2 RT groups were not significant \((P=0.10–0.86; Table 3)\); however, the recovery rate values for the higher-intensity RT group were generally higher than those for the lower-intensity RT group.

Interaction Between Initial Motor Status and Treatment Intensity
Figure 3 shows the relationships between patients’ baseline scores and change scores on the FMA. The data fit a quadratic function, and the critical point of the fitted curve in the higher-intensity RT group at posttreatment was calculated to be 38.41 by differentiating the equation of the curve (Figure 3); that is, patients with an FMA baseline score of approximately 40 showed the most gains after the higher-intensity RT. In the lower-intensity RT group, patients with fewer motor deficits gained more benefits on the FMA; however, the general gains of this group were lower than the gains in the higher-intensity RT group. To summarize, the patients with motor deficits in the middle range (FMA score of approximately 40) showed more improvement in motor ability after the higher-intensity RT than those with severe or mild motor deficits.

Discussion
The 3 treatment groups in this trial had significant within-group gains on the FMA, Medical Research Council, and Motor Activity Log, indicating that the patients benefited from the intervention in motor ability, muscle power, and self-perceived performance in daily activities. The 2 RT groups also reported significant improvements in the strength domain of the SIS over time. Between-group comparisons showed that the patients who received the higher-intensity RT had significant improvements in primary motor ability at mid-term and posttreatment compared with those who received the lower-intensity RT or CT; however, the 2 RT protocols and the CT demonstrated comparable effects on improving the secondary outcomes.

When these results were compared with those in the trial by Hesse et al,14 which used the same robotic device, the effects on the primary outcome (ie, FMA) were different. The treatment intensity of RT used in their study was similar to the lower-intensity RT used in this study. The RT group in the Hesse et al study, however, had significant benefits compared with the control group, whereas we did not find a significant difference between the lower-intensity RT and the CT. The differing results may be attributable to differences in treatment protocols of the control groups (electric stimulation versus conventional occupational therapy), stroke phases (subacute versus chronic), and baseline motor deficits of patients (severe versus mild to moderate). Moreover, the higher-intensity RT (twice as many repetitions as in the lower-intensity RT) of this study led to significant gains in motor ability compared with the other 2 groups. Our findings suggest that for patients with chronic stroke with mild to moderate motor deficits, the treatment intensity of RT using the Bi-Manu-Track can be higher than the original protocol14 to reach superior effects on motor recovery.
The study results for the functional-based or disability outcomes are concordant with previous RT studies that did not find significant differences between RT and control groups. Within-group analyses, however, showed that the 2 RT groups had significant gains in self-perceived amount of use and quality of movement of the affected hand in daily activities and in the strength domain of the SIS evaluation. These gains may be attributed to the additional 15 to 20 minutes of functional training per session in our RT protocols. The supplementary functional practice may be necessary to enhance functional performance but may not be sufficient for significant between-group differences compared with the CT. Most robotic devices are designed for the practice of relatively simple movements, and patients who train on them have some difficulty in transferring the gained motor ability to the performance of functional activities. Further approaches may consider the combination of RT and task-oriented training (eg, constraint-induced therapy) in stroke rehabilitation to promote motor recovery and functional improvement.

The recovery rate data suggest a trend for better motor outcome with the higher-intensity RT at midterm and posttreatment, indicating a dose–response relationship such that providing more intense RT may accelerate motor improvement for chronic stroke. Current findings support that highly intensive therapy tends to accelerate recovery. The midterm evaluation can provide more information about the dynamic response of patients during the treatment course; however, whether the intensity effect occurs mainly in the first half or throughout the entire period of the treatment course needs further research. For patients who have already reached a functional plateau at midterm, incorporating or receiving other interventions after midterm (eg, RT in sequential combination with constraint-induced therapy) might promote further improvement.

The initial severity levels of the patients may influence the treatment effects on the primary outcome. The FMA is commonly used to identify the severity levels of patients with stroke. The relation of FMA baseline scores and change scores in this study was dependent on the intensity of RT treatment. As seen in the graph (Figure 3), patients with moderate motor deficits (ie, FMA score of approximately 40) showed more motor improvement after the higher-intensity RT than those with severe or mild deficits. However, there was a trend that the patients with fewer motor deficits in the lower-intensity RT group gained more benefits on the FMA.

Some limitations of the study warrant consideration. Only one intermediate assessment was conducted during the study period. To more clearly define dose–response curves of RT, further investigation of the efficacy of RT on multiple intermediate data points is warranted. This study did not evaluate sensory function. Patients with sensory deficits who receive interactive RT with sensory inputs and feedback may benefit from RT. Further trials should assess the role of sensory function as a treatment outcome and potential moderator of the outcomes. Another study limitation is that the participants and the intervention providers were not blinded to the treatment group, which might have led to some bias.

In conclusion, our study results support that treatment outcomes, especially in motor improvements, were better after the higher-intensity RT than after the other 2 interventions. Higher-intensity RT may be feasible in patients with...
chronic stroke to accelerate the rate of motor recovery. Patients with moderate motor deficits tended to have more motor improvements after the higher-intensity RT than those with severe or mild motor deficits. The patient’s level of motor impairment should be considered when planning for robot-assisted stroke rehabilitation.

Sources of Funding
This project was supported in part by the National Health Research Institutes (NHRI-EX101-9920PI and NHRI-EX101-10010PI), the National Science Council (NSC-100-2314-B-002-008-MY3 and NSC-99-2314-B-182-014-MY3), and the Healthy Ageing Research Center at Chang Gung University (EMRPD1A0891) in Taiwan.

Disclosures
None.

References
Dose–Response Relationship of Robot-Assisted Stroke Motor Rehabilitation: The Impact of Initial Motor Status
Yu-wei Hsieh, Ching-yi Wu, Keh-chung Lin, Grace Yao, Kuen-yuh Wu and Ya-ju Chang

Stroke. 2012;43:2729-2734; originally published online August 14, 2012;
doi: 10.1161/STROKEAHA.112.658807
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/43/10/2729

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/