Upper Limb Robotic Rehabilitation After Stroke: A Multicenter, Randomized Clinical Trial

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Background and Purpose: After stroke, only 12% of survivors obtain complete upper limb (UL) functional recovery, while in 30% to 60% UL deficits persist. Despite the complexity of the UL, prior robot-mediated therapy research has used only one robot in comparisons to conventional therapy. We evaluated the efficacy of robotic UL treatment using a set of 4 devices, compared with conventional therapy.

Methods: In a multicenter, randomized controlled trial, 247 subjects with subacute stroke were assigned either to robotic (using a set of 4 devices) or to conventional treatment, each consisting of 30 sessions. Subjects were evaluated before and after treatment, with follow-up assessment after 3 months. The primary outcome measure was change from baseline in the Fugl-Meyer Assessment (FMA) score. Secondary outcome measures were selected to assess motor function, activities, and participation.

Results: One hundred ninety subjects completed the posttreatment assessment, with a subset (n = 122) returning for follow-up evaluation. Mean FMA score improvement in the robotic group was 8.50 (confidence interval: 6.82 to 10.17), versus 8.57 (confidence interval: 6.97 to 10.18) in the conventional group, with no significant between-groups difference (adjusted mean difference −0.08, $P = 0.948$). Both groups also had similar change in secondary measures, except for the Motricity Index, with better results for the robotic group (adjusted mean difference 4.42, $P = 0.037$). At follow-up, subjects continued to improve with no between-groups differences.

Discussion and Conclusions: Robotic treatment using a set of 4 devices significantly improved UL motor function, activities, and participation in subjects with subacute stroke to the same extent as a similar amount of conventional therapy. Video Abstract is available for more insights from the authors (see the Video, Supplemental Digital Content 1, available at: http://links.lww.com/JNPT/A291).

Key words: *randomized controlled trial, rehabilitation, robotics, stroke, upper extremity*

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INTRODUCTION

Only 12% of stroke survivors obtain complete upper limb (UL) functional recovery after 6 months from stroke.[1] In the remaining 88%, UL motor deficits persist with a

negative impact on their level of activities[2-4] and participation,[5] according to the International Classification of Functioning, Disability and Health (ICF).[6]

Robotic therapy has been proposed as a viable approach for the rehabilitation of the UL, as a way to increase the amount and intensity of the therapy,[7] and to standardize the treatment,[8] by providing complex but controlled multisensory stimulation.[7] Moreover, because of their built-in technology in terms of sensors and actuators, robotic devices can provide quantitative measure about the user's dexterity.[9] A large number of scientific articles on robot-assisted rehabilitation after stroke have been published, analyzing the effects of robotics alone,[10-18] or in conjunction with conventional therapy.[19-24] Nowadays, the use of robotic rehabilitation in addition to conventional therapy is recommended in some of the current stroke guidelines.[25]

Regarding the efficacy of robotic rehabilitation when compared with other treatments, the available scientific data are not conclusive. In comparing robotic and conventional treatment, some studies did not find an overall significant effect in favor of robotic therapy[11,26,27]: others showed a greater effect of robotic therapy than conventional therapy.[28] However, in the latter case, the results must be interpreted with caution because the quality of the evidence was low or very low, owing to the variations between the trials in intensity, duration, and amount of training, type of treatment, participant characteristics, and measurements used. Finally, according to the most recent meta-analysis,[29] it is not clear whether the difference between robotic therapy and other interventions (as conventional therapy) is clinically meaningful for the persons with stroke.

Almost all studies of robotic therapy have focused on the effects of the use of 1 device, compared with a conventional therapy approach. However, despite the complexity of the anatomy and the motor function of whole UL, especially the hand, almost all commercial devices act on a limited number of joints and a limited workspace. Conversely, during conventional therapy, the whole UL is routinely treated and the 3-dimensional space explored. Because of this, it is very difficult to compare the effects of 1 robotic device with conventional approaches. Therefore, it would be desirable to use devices that allow treatment of the entire UL (from shoulder to hand), in a workspace similar to that required in daily activities. Moreover, using more than 1 device new personnel organizational models can be adopted, wherein 1 physical therapist supervises more than 1 patient, thereby increasing the sustainability of the treatment.[15,21,30]

The aim of the current study was to evaluate, in subjects with subacute stroke, the efficacy of standardized UL robotic rehabilitation (using an organizational model in which 1 physical therapist supervises 3 subjects, each treated using a set of 4 robots and sensor-based devices), compared with UL conventional therapy. Outcomes of interest were selected to reflect effects on function, activities, and participation (per the ICF)

METHODS

Study Design and Participants

We conducted a multicenter, randomized (1:1), controlled, parallel group clinical trial to compare a robotic rehabilitation approach with a traditional individual conventional physical therapy approach in subjects with stroke. The study was conducted in 8 rehabilitation centers of the Fondazione Don Carlo Gnocchi, in Italy, from August 2016 to March 2018.[31]

We recruited consecutive subjects with 1 ischemic or hemorrhagic stroke (verified by MRI or CT), aged between 40 and 85 years, with a time since stroke ranging from 2 weeks to 6 months (ie, after the acute phase)[1] and cognitive and language abilities adequate to understand the experiments and the follow instructions. Subjects' upper extremity Fugl-Meyer Assessment (FMA) score (0-66 version) had to be 58 or less. Exclusion criteria were behavioral and cognitive disorders and/or reduced compliance, fixed contraction in the affected limb (ankylosis, Modified Ashworth Scale equal to 4), and severe deficits in visual acuity. The study was conducted in accordance with the International Conference on Harmonization Good Clinical practice guidelines and the Declaration of Helsinki. All participants gave written informed consent prior to study participation. The institutional Ethics and Experimental Research Committee of the Fondazione Don Carlo Gnocchi approved the study protocol on April 6, 2016 (FDG_6.4.2016). The study is registered with ClinicalTrials.gov (NCT02879279). The first subject of the current study was enrolled on August 18, 2016. Between May 2016 and the Trial Registration Date (August 11, 2016), we evaluated the feasibility of the protocol in a small sample. Data obtained from subjects enrolled during this period were not analyzed. Based on this preliminary enrollment, we found that a high percentage of eligible subjects would have been excluded only because of older than 80 years. Therefore, an amendment was proposed and accepted by the ethical committee (September 2016) to extend eligibility to subjects aged up to 85 rather than 80 years, as originally proposed.

Intervention

Eligible subjects were randomly assigned either to an experimental group (robotic group, RG) or to a control group (conventional group, CG). Randomization sequence was generated by using the R (version 3.3.0, R Core Team, Vienna, Austria) package *blockrand*, with random block sizes ranging from 2 to 8. Randomization was stratified according to disease onset (early onset, $\leq$3 months; late onset, $>$3 months) and age (younger, 40-60 years; older, $>$60 years), to ensure that the numbers and subjects' characteristics in each group were closely matched. The randomization list was prepared by an investigator with no clinical role in the study.

Robotic Group

In the RG, both the distal and the proximal segments of the subjects' UL were treated by means of robotic and sensor-based devices. Specifically, subjects were treated with the following systems: (*a*) a robotic device that allows passive, active, and active-assistive planar movements of the shoulder and elbow joints (Motore, Humanware, Italy); (*b*) a robotic device that allows passive, active, and active-assistive finger flexion and extension movements (Amadeo, Tyromotion, Austria); (*c*) a sensor-based system that allows unsupported 3-dimensional movements of shoulder, elbow, and wrist joint, both unimanual and bimanual (Pablo, Tyromotion, Austria); and (*d*) a robotic

system that allows 3-dimensional, unimanual and bimanual, movements of the shoulder joint, with arm weight support (Diego, Tyromotion, Austria). During the treatment, subjects performed both motor and cognitive tasks, and the devices provided visual and auditory feedback. In addition, a vibratory treatment (with a frequency of 60 Hz) was applied, using the Amadeo system, to increase the proprioception of the hand, before the finger training.[32] The experimental treatment was aligned among the centers in terms of protocol and intensity. During the treatment, a group of 3 subjects was supervised by 1 therapist. During each session, the physical therapist used 1 system for each subject, to minimize the time required to move the subjects from one system to another. The rehabilitation program started with the robotic device for the shoulder and elbow joints, followed by the robotic device for the hand, the sensor-based device for the shoulder, elbow, and wrist, and, finally, the robotic system for the shoulder. The adopted protocol provided general guidelines, which were organized into a flowchart, in order to ensure the homogeneity of treatment. However, the physical therapist selected and adapted the exercises, in term of workspace and difficulty, to the subject's residual ability. More details about the robotic treatment are reported in the Appendix (see Supplemental Digital Content 2, available at: http://links.lww.com/JNPT/A292).

Conventional Group

In the CG, subjects underwent a conventional treatment, with a ratio of 1 therapist to 1 subject, that followed the guidelines provided in literature.[33,34] The therapeutic task focused on functional improvement, including task-oriented exercises, sensorimotor reorganization, and spasticity inhibition. Subjects performed passive, active, and active-assisted exercises on the 3 UL joints, in the 3-dimensional space, to improve joint function, to prevent contractures, to inhibit spasticity, and to improve motor function. The therapeutic task focused on functional improvement, sensorimotor reorganization, and spasticity inhibition. Subjects performed passive, active, and active-assisted exercises on the 3 UL joints, in the 3-dimensional space to gain strength and motor function, improve joint range of motion, prevent contractures, and inhibit spasticity. They also performed task-oriented exercises included reaching and grasping movements (eg, reaching and picking up a glass or other objects), activities of daily living (eg, transfers, dressing, brushing/combing hair, according to subject's ability), to increase the subject's participation so as to promote neuroplasticity and improve upper limp motor recovery. At the first treatment session each subject underwent an UL evaluation aimed to personalize the rehabilitation program and determine the exercises to deliver. Each therapist was free to adapt every rehabilitation session to the subject, according to their functional assessment and needs. Therefore, each activity duration, specific number of repetitions or difficulty of exercise to be performed during a conventional rehabilitation session was not predefined in the protocol.

Specifically, the intervention adopted in the protocol included repetitive practice of the following activities: soft tissue mobilization (effleurage, lymph drainage techniques, myofascial release); joint mobilization (passive, active-assisted, active movements); facilitation of muscle activity movement (active-assisted movement, mental imagery, subject/therapist generated cueing, facilitated arm/hand activity from another body part, restricted use of nonparetic UL); mobility/transfer training (moving into different positions including supine lying, side-lying nonhemiplegic/hemiplegic side, transferring to and sitting in wheelchair/armchair); specific sensory input (tactile and proprioceptive stimulation); splinting techniques (shoulder, elbow, wrist/hand support); strengthening (resistance from body weight or physical therapist or equipment, gravity neutral repetitive movement); balance and mobility incorporating UL activity (in or from lying/sitting/standing, in walking); UL functional tasks (unilateral reaching activities, bilateral functional activities, dexterity exercises); and education for the subject and carer (transfers training, self-monitoring/handling/positioning of UL).

In both groups, the treatment was performed daily for 45 minutes, 5 days a week, for a total of 30 sessions. In addition to the UL rehabilitation session (according to the allocated group), all subjects underwent conventional rehabilitation sessions (6 times/week), lasting 45 minutes, focused on lower limb, sitting and standing training, balance, and walking. Subjects underwent occupational and speech therapy, if needed. To avoid the possibility of performance bias, the therapists who treated the subjects in the RG were different from therapists who treated the subjects in the CG.

Evaluation Timing

Subjects were evaluated at baseline (T0), after treatment (T1), and 3 months after the end of the treatment (T2). To be included in the analysis, subjects had to undergo at least 25 rehabilitation sessions, and they could not interrupt the treatment (due to clinical complications) for more than 6 consecutive sessions; otherwise, they were considered as dropouts.

Outcome Measures

The primary outcome was the change from baseline after the treatment of the UL motor function domain of the Fugl-Meyer Assessment of Sensorimotor Recovery after Stroke.[35] The FMA upper extremity motor function domain assesses the severity of UL motor impairment and consists of 22 items that are summed to produce an overall score, ranging from 0 (worst, completely plegic) to 66 (best, normal). The evaluators who performed the primary outcome assessment were blinded to the treatment assignment. To reduce variability in the primary outcome assessment, the administration of the Fugl-Meyer was video recorded by a trained operator, and then sent to the coordinating study center where 2 operators, blinded to group allocation, evaluated all the recorded video.

Secondary outcomes were the changes from baseline after the treatment of the following clinical scales: Motricity Index (MI)[36]; Medical Research Council (MRC)[37]; Modified Ashworth Scale (MAS)[38]; Neuropathic Pain Diagnostic Questionnaire (DN4)[39]; Numerical Rating Scale of pain (NRS)[40]; modified Barthel Index (mBI)[41]; Frenchay Arm Test (FAT)[42]; Action Research Arm Test (ARAT)[43]; and 36-item Short Form

Health Survey (SF36)—Physical Composite Score (PCS) and the Mental Composite Score (MCS).[44] Secondary outcomes were evaluated in each center by the local physical therapists, who were specifically trained; therefore, although intended, masking of assessors could not be guaranteed. The outcomes were chosen, according to the ICF domains,[45,46] to evaluate (*a*) body function (FMA, MI, MRC, MAS, DN4, NRS); (*b*) activities (mBI, FAT, ARAT); and (*c*) participation (SF36—PCS and MCS).

Secondary analyses assessed the persistence of treatment effects, using the previously mentioned outcome measures at a follow-up evaluation 3 months after the end of the treatment. In addition, using the primary outcome measure, we assessed the treatment effect in subgroups of subjects (according to disease onset and level of impairment). In addition, we analyzed changes in the separate Fugl-Meyer subscores. Finally, we investigated the possible predictors of motor recovery after rehabilitation.

Statistical Analyses

Sample size was calculated by means of a 2-sided, 2-sample *t* test assuming: 90% power; type I error of 0.05; a mean difference of 5 units on the FMA,[47] a common standard deviation of 10 points.[48] Considering a dropout rate of 20%, the final sample size required was estimated to be 224 cases. Statistical analysis was performed using commercial statistical software (SPSS version 25, IBM, New York).

For the primary analysis, the changes from baseline of the FMA over the treatment period (T1-T0) were compared in the 2 groups, using analysis-of-covariance models, adjusting for the baseline value. The same analysis was performed for all the secondary outcome measures.

For the secondary analyses, 2-way mixed analysis of variance (ANOVA) tests, with *group* (2 levels: conventional and robotic) as between factor and *time* (3 levels: T0, T1, and T2) as within factor, were used. When the main effect *time* was significant, pairwise comparisons with Bonferroni correction were tested. In addition, using analysis-of-covariance models, adjusting for the baseline value, we compared the changes from baseline of the primary outcome measure over the treatment period (T1-T0) in the following subgroups: (*a*) early onset (<3 months) versus late onset (>3 months); and (*b*) severe versus moderate versus mild, according to the baseline value of the FMA. In addition, we compared the changes from baseline of the subitems of the primary outcome measure (proximal, distal, and coordination) over the treatment period (T1-T0) in the 2 groups. Finally, to identify possible predictors of recovery after rehabilitation, we categorized the subjects as improved (changes from baseline of the FMA ≥ 5 points) or not improved (changes from baseline of the FMA < 5 points) after the treatment and we then conducted a multivariable logistic regression with the following candidate predictors: age, time since stroke, affected side, type of stroke, treatment, and baseline value of the FMA.

All the analyses were done according to a modified intention-to-treat analysis, including all participants for which data were available. For all statistical tests, the significance level was set at $\alpha < 0.05$.

RESULTS

Sample

Between August 2016 and October 2017, 631 subjects were assessed for eligibility (Figure 1).

The most common reason for exclusion was the age (131 subjects, 34.1%), an FMA score higher than 58 (123 subjects, 32%), cognitive and language deficits (120 subjects, 31.3%), and a time since stroke outside inclusion criteria range (119 subjects, 31%). Less frequently subjects were excluded because of recurrent stroke (41 subjects, 10.7%), a MAS equal to 4 (19 subjects, 4.9%), or visual deficits (5 subjects, 1.3%). It is noteworthy that, in 35.3% of subjects, more than 1 exclusion criteria were present. According to the inclusion criteria, 247 subjects were enrolled and randomized to either the RG or the CG. Twelve randomized subjects in the RG and 11 subjects in the CG never received the allocated intervention, due to a worsening of the clinical condition before their baseline assessment. Therefore, 224 subjects had a baseline evaluation and received the allocated intervention (111 in the RG and 113 in the CG). Thirty-four subjects (20 in the RG and 14 in the CG) did not complete at least 25 rehabilitation sessions due to a worsening of the clinical condition and were considered dropouts. None of the dropouts was due to adverse events or dissatisfaction with type of treatment received. Therefore, 190 subjects were evaluated after the treatment (T1) and considered for the primary analysis. Finally, 68 subjects did not return for the follow-up visit; hence, a total of 122 subjects were assessed during the follow-up for the secondary analysis. The low rate of subjects turning up for a follow-up was due to the fact they lived too far away from the center or did not have anyone that could assist them in getting to the center, and not to adverse events or dissatisfaction with the type of treatment received. This study was funded only by the Fondazione Don Carlo Gnocchi and no financial support was available for the subject's assistance and transfer.

Baseline Characteristics

Baseline characteristics are summarized in Table 1. The 2 groups were comparable in terms of age, time from onset to randomization, sex, index stroke type and location, affected side, and neglect syndrome. A higher percentage of subjects in the CG showed language impairment.

Primary Analysis

After the treatment, the mean change of the FMA was 8.50 points in the RG and 8.57 points in the CG (Table 2), higher than the Minimal Clinically Important Difference (MCID) of the scale (5 points).[47] According to the statistical analysis, this improvement, adjusted for baseline, was comparable ($P = 0.948$); therefore, the primary outcome measure failed to detect a difference between the 2 groups.

The change from baseline of the primary outcome measure for each subject, as function of her/his baseline FMA value, is depicted by the scatterplot in Figure 2.

As reported in Table 2, the differences in mean changes, adjusted for baseline, were similar in all the outcome measures except the MI; for the latter, a greater improvement was detected in the RG, when compared with the conventional

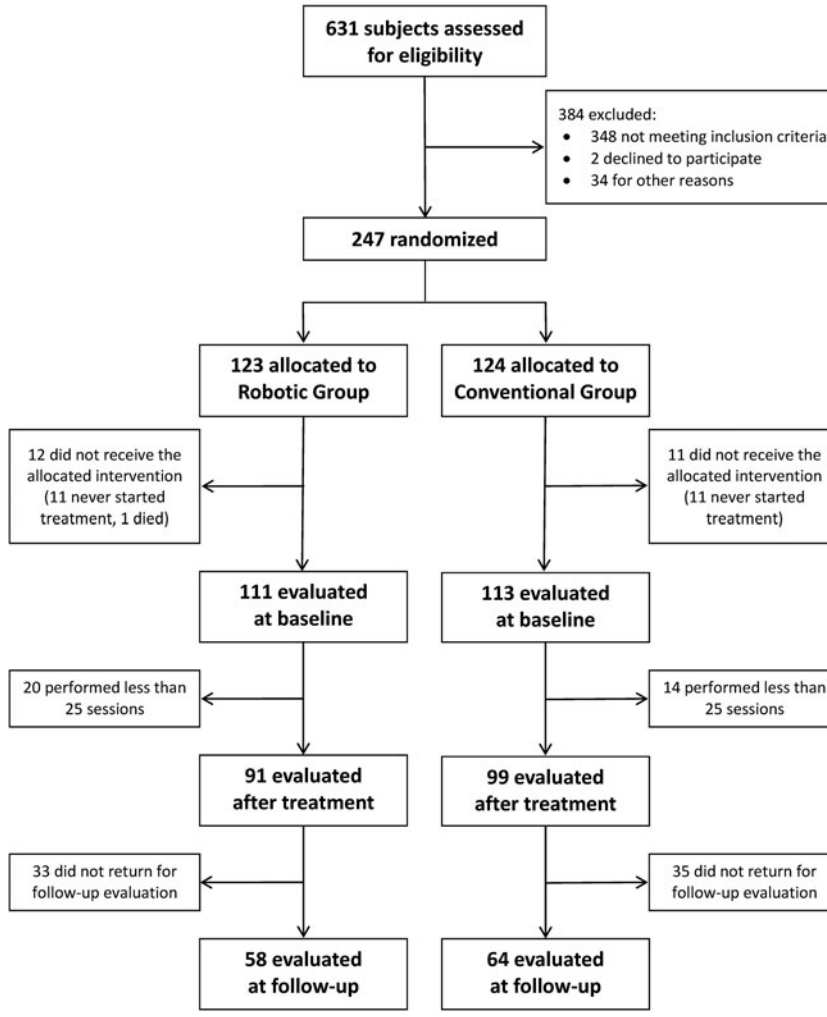

Figure 1. CONSORT Diagram.

one (mean difference 4.42; 95% confidence interval 0.27-8.57; $P = 0.037$).

Secondary Analysis

With respect to the follow-up evaluation (3 months after the end of the treatment), the interaction factor time×group was not significant for all the investigated outcome measures (see Table 3).

The main effect time was significant ($P < 0.001$) for the following outcome measures: FMA, MI, mBI, MRC for shoulder, elbow, and wrist, FAT, ARAT, MAS for the elbow, PCS, and MCS. Post hoc analysis revealed that all the time points were different from the others, except for the MAS at the elbow, where the difference lied between the first and the last evaluation, and the MCS, where the difference lied between T0 and T1, and between T0 and T2 (see also Figure 3).

No differences between the RG and the CG were identified when grouping the subjects according to time since stroke ($P = 0.910$ for both subgroups), or according to baseline impairment (severe: $P = 0.226$; moderate: $P = 0.410$; and mild: $P = 0.108$) as reported in Figure 4. Similarly, we did not find differences when considering the separate subscores of the FMA (proximal: $P = 0.954$; distal: $P = 0.431$; and coordination: $P = 0.260$).

The logistic regression analysis showed that the variables that predicted recovery were the age and the baseline impairment, as measured by the FMA (Table 4).

DISCUSSION

In this study, we aimed to evaluate the efficacy of a robotic UL treatment, using a set of 4 devices, compared with conventional therapy. This multicenter randomized controlled trial showed that, in subjects with subacute stroke, robotic-assisted therapy using a set of robotic and sensor-based devices significantly improved UL motor function, activities, and participation to the same extent as a similar amount of conventional therapy. In fact, according to the primary outcome measure, no significant difference was observed between the 2 investigated groups.

Several studies have previously been conducted to compare a robotic treatment with a conventional approach.

Table 1. Baseline Characteristics of the Sample[a]

Characteristics	Robotic Group (n = 111)	Conventional Group (n = 113)
Age, y	69.5 (10.9)	68.5 (11.5)
Sex		
Men	63 (56.8%)	64 (56.6%)
Women	48 (43.2%)	49 (43.4%)
Index stroke type		
Ischemic	81 (73.0%)	84 (74.3%)
Hemorrhagic	30 (27.0%)	29 (25.7%)
Index stroke location (ischemic stroke)		
Lacunar stroke	12 (14.8%)	12 (14.3%)
Partial anterior circulation stroke	46 (56.8%)	53 (63.1%)
Total anterior circulation stroke	8 (9.9%)	9 (10.7%)
Posterior circulation stroke	15 (18.5%)	10 (11.9%)
Affected side		
Right	48 (43.2%)	58 (51.3%)
Left	63 (56.8%)	55 (48.7%)
Language impairment	14 (12.6%)	31 (27.4%)
Neglect syndrome	22 (19.8%)	24 (21.2%)
Days from index stroke to enrollment	48.0 (41.1)	45.3 (40.6)
15-30 d	57 (51.4%)	60 (53.1%)
31-90 d	39 (35.1%)	36 (31.9%)
91-180 d	15 (13.5%)	17 (15.0%)
Strata		
Younger, early onset	21 (18.9%)	23 (20.4%)
Younger, late onset	6 (5.4%)	5 (4.4%)
Older, early onset	72 (64.9%)	74 (65.5%)
Older, late onset	12 (10.8%)	11 (9.7%)
Body function		
Fugl-Meyer Upper Extremity Motor Function Score (0-66)	25 (16.5)	21.8 (16.2)
Severe (0-28)	63 (56.7%)	72 (63.7%)
Moderate (29-42)	26 (23,4%)	25 (22.1%)
Mild (43-66)	22 (19.9%)	16 (14,2%)
Motricity Index Upper Limb (0-100)	37.6 (27.6)	33.2 (28.8)
Medical Research Council Scale (0-5)		
Shoulder	2 (1.4)	1.6 (1.5)
Elbow	1.9 (1.6)	1.6 (1.6)
Hand	1.7 (1.6)	1.5 (1.6)
Modified Ashworth Scale (0-4)		
Shoulder abduction	0.3 (0.6)	0.3 (0.7)
Shoulder intrarotation	0.3 (0.7)	0.4 (0.7)
Elbow	0.6 (0.9)	0.5 (0.8)
Wrist	0.5 (0.8)	0.4 (0.7)
Numerical Rating Scale (0-10)	2.8 (2.9)	2.6 (2.7)
Douleur Neuropathique 4 (0-10)	1.7 (1.9)	1.7 (1.8)
Activities		
Modified Barthel Index (0-100)	34.3 (25.8)	33 (27.5)
Frenchay Arm Test (0-5)	1.3 (1.8)	1.1 (1.7)
Action Research Arm Test (0-45)	12.4 (15.3)	10.4 (13.9)
Participation		
Short-Form 36—Physical Composite Score (0-100)	28.6 (7.2)	28.1 (6.7)
Short-Form 36—Mental Composite Score (0-100)	41.8 (12.2)	40 (12)

[a]Data are mean (SD) or n (%).

However, most of them investigated the effects of robotics in conjunction with conventional therapy; therefore, they could not attribute the outcomes to robotic therapy, and cannot be directly compared with our study. With respect to the studies wherein robotic rehabilitation alone (without an additional conventional therapy intervention) was compared with conventional therapy alone, most of these studies did not detect differences between groups.[11,14,15] Some studies show results in favor of robotic therapy, but the differences are always small and of weak significance.[10,13,16,17] According to our primary outcome measure, we did not find differences between the 2 approaches; therefore, our results confirm the literature indicating that both robotic therapy and conventional therapy improve UL function in persons with subacute stroke, and the outcomes are equivalent.

Analyzing the secondary outcome measures, we found a higher UL muscle strength improvement (according to the MI) in the RG at the end of the treatment. Finally, subjects continued to improve in UL motor function, activities, and

Table 2. Changes in Outcome Between Baseline and End of the Treatment

	Robotic Group		Conventional Group		Mean (95% CI) Difference Between Groups	
	N	Mean Change (95% CI) From Baseline Adjusted[a]	N	Mean Change (95% CI) From Baseline Adjusted[a]	Adjusted[a]	*P* Value
Primary outcome						
Fugl-Meyer Assessment	91	8.50 (6.82 to 10.17)	99	8.57 (6.97 to 10.18)	− 0.08 (−2.40 to 2.24)	0.948
Secondary outcomes						
Motricity Index	91	17.35 (14.35 to 20.34)	99	12.92 (10.05 to 15.79)	4.42 (0.27 to 8.57)	*0.037*
Modified Barthel Index	91	23.87 (20.02 to 27.73)	99	22.98 (19.28 to 26.67)	0.90 (−4.44 to 6.24)	0.74
MRC						
Shoulder	91	0.75 (0.57 to 0.92)	99	0.70 (0.53 to 0.87)	0.05 (−0.20 to 0.30)	0.701
Elbow	91	0.93 (0.73 to 1.13)	99	0.78 (0.59 to 0.97)	0.15 (−0.13 to 0.42)	0.287
Wrist	91	0.69 (0.49 to 0.88)	99	0.71 (0.52 to 0.90)	− 0.03 (−0.30 to 0.25)	0.835
Frenchay Arm Test	91	0.87 (0.58 to 1.16)	99	0.88 (0.60 to 1.15)	0.00 (−0.41 to 0.40)	0.988
Action Research Arm Test	91	6.04 (4.26 to 7.83)	99	6.70 (4.84 to 8.57)	0.66 (−1.92 to 3.25)	0.613
Numerical Rating Scale	91	0.05 (−0.43 to 0.54)	99	− 0.30 (−0.76 to 0.17)	0.35 (−0.32 to 1.02)	0.306
Douleur Neuropathique 4	91	− 0.08 (−0.40 to 0.24)	99	− 0.19 (−0.49 to 0.11)	0.11 (−0.33 to 0.55)	0.617
Modified Ashworth Scale						
Shoulder abduction	91	0.02 (−0.10 to 0.14)	99	0.07 (−0.05 to 0.18)	− 0.05 (−0.21 to 0.12)	0.568
Shoulder intrarotation	91	0.02 (−0.10 to 0.15)	99	0.03 (−0.09 to 0.15)	− 0.01 (−0.18 to 0.16)	0.901
Elbow	91	0.11 (−0.03 to 0.26)	99	0.15 (0.01 to 0.29)	− 0.04 (−0.24 to 0.16)	0.707
Wrist	91	0.01 (−0.11 to 0.14)	99	0.02 (−0.10 to 0.14)	− 0.01 (−0.18 to 0.17)	0.941
SF36—PCS	89	1.66 (0.48 to 2.84)	91	1.37 (0.20 to 2.54)	0.29 (−1.37 to 1.95)	0.729
SF36—MCS	89	3.15 (1.18 to 5.11)	91	4.46 (2.52 to 6.40)	− 1.32 (−4.08 to 1.45)	0.348

Abbreviations: CI, confidence interval; MCS, Mental Composite Score; MRC, Medical Research Council; PCS, Physical Composite Score; SF36, 36-item Short Form Health Survey.
[a]Adjusted for baseline value. Values in *italics* indicate a statistically significant difference ($P < 0.05$).

participation at the follow-up, 3 months after the end of the treatment, without differences between the groups.

This is the first study including such a wide sample of subacute stroke survivors: more than 600 eligible subjects were evaluated, 247 of them randomized, and 224 subjects treated in a period of 18 months—thanks to the participation of 8 collaborating centers. As reported by other authors, although UL impairment in stroke is common, recruitment of subjects can be difficult and sometimes the target enrollment cannot be achieved at the end of the planned enrollment period mainly in rehabilitation clinical trials.[48] In our study, we tried to avoid relatively tight selection criteria but there are challenges to having both a homogeneous sample (to follow a rigorous scientific approach) and a real sample (to observe the daily clinical practice subjects) at the same time. To recruit a wide but also real sample, we included subjects with hemorrhagic or ischemic stroke, as well as subjects with a complete UL plegia (Fugl-Meyer <10); we excluded only subjects with an UL performance (Fugl-Meyer >58) that would render the treatment unnecessary. This choice allowed us to observe a clinically meaningful improvement (an increase of FMA ≥ 5) also in subjects with FMA at baseline lower than 10.

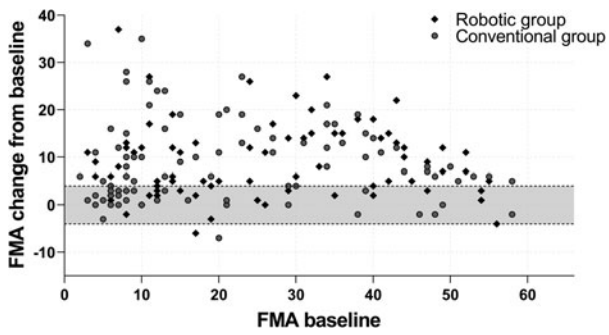

Figure 2. Scatterplot of the changes from baseline of the FMA for each patient, as function of their baseline value. The area between the 2 dotted lines encloses subjects without a clinically meaningful change of the FMA (<5 points). FMA, Fugl-Meyer Assessment.

Regarding time since stroke, we decided to include subjects with latency from 15 days to 6 months from the stroke for 3 reasons: (*a*) an important previous scientific study in this field was conducted on participants with chronic stroke (time since stroke >6 months)[11]; (*b*) the greatest functional recovery occurs within 6 months after stroke,[49] and this is particularly true for UL recovery[50]; and (*c*) the participating centers treat mainly patients with stroke with this latency from onset.

After treatment, subjects in the RG improved in muscle strength (as measured by MI) significantly more than subjects in the CG. Our hypothesis is the robotic therapy allows a higher number of repetitions and, therefore, a more intensive training, with possible effects on muscle strength. Our findings about the progressive improvement observed at the follow-up, 3 months after the end of the treatment, in both groups (RG and CG) in UL motor function, activities, and participation are noteworthy. After 30 experimental sessions focused on the UL treatment, subjects continued with only the usual conventional rehabilitation sessions (which focused on paretic limb treatment, sitting and standing training, balance, and walking recovery). The first 6 months is confirmed to be very important

Table 3. Secondary Analysis (Follow-up Evaluation)

	Robotic Group				Conventional Group				Mixed ANOVA (*P* Value)			Post Hoc (*P* Value)		
	N	T0 Mean (95% CI)	T1 Mean (95% CI)	T2 Mean (95% CI)	N	T0 Mean (95% CI)	T1 Mean (95% CI)	T2 Mean (95% CI)	Time	Group	Time × Group	T0 vs T1	T0 vs T2	T1 vs T2
Fugl-Meyer Assessment	58	25.9 (21.7 to 30.1)	35.4 (30.7 to 40)	39.8 (35.3 to 44.4)	64	21.1 (17.1 to 25.2)	31.7 (27.2 to 36.1)	37.7 (33.3 to 42.1)	*<0.001*[a]	0.235	0.368	*<0.001*	*<0.001*	*<0.001*
Motricity Index	58	38.8 (31.8 to 45.8)	56.7 (49.4 to 63.9)	64.0 (56.8 to 71.2)	64	32.6 (26.0 to 39.3)	47.6 (40.7 to 54.4)	59.4 (52.5 to 66.2)	*<0.001*	0.158	0.312	*<0.001*	*<0.001*	*<0.001*
Modified Barthel Index	58	36.6 (29.6 to 43.6)	60.1 (53.1 to 67.2)	75.5 (69.2 to 81.7)	64	31.3 (24.6 to 37.9)	58.4 (51.7 to 65.1)	73.9 (67.9 to 79.8)	*<0.001*	0.493	0.534	*<0.001*	*<0.001*	<0.001
Medical Research Council														
Shoulder	58	2.0 (1.6 to 2.4)	2.7 (2.3 to 3.1)	3.1 (2.8 to 3.5)	64	1.6 (1.2 to 1.9)	2.5 (2.2 to 2.9)	3.0 (2.6 to 3.3)	*<0.001*	0.279	0.308	*<0.001*	*<0.001*	*<0.001*
Elbow	58	2.0 (1.6 to 2.4)	2.9 (2.5 to 3.3)	3.3 (2.9 to 3.7)	64	1.6 (1.2 to 2)	2.6 (2.2 to 3)	3.3 (2.9 to 3.7)	*<0.001*	0.393	0.144	*<0.001*	*<0.001*	*<0.001*
Wrist	58	1.7 (1.3 to 2.2)	2.5 (2.1 to 2.9)	2.9 (2.5 to 3.3)	64	1.5 (1.1 to 1.9)	2.3 (1.9 to 2.7)	2.7 (2.3 to 3.1)	*<0.001*	0.420	0.878	*<0.001*	*<0.001*	*<0.001*
Frenchay Arm Test	58	1.2 (0.8 to 1.6)	2.2 (1.6 to 2.7)	2.7 (2.2 to 3.3)	64	1.0 (0.6 to 1.4)	2.0 (1.5 to 2.5)	2.7 (2.1 to 3.2)	*<0.001*	0.659	0.867	*<0.001*	*<0.001*	*<0.001*
Action Research Arm Test	58	12.3 (8.5 to 16.2)	20.6 (16.2 to 24.9)	23.9 (19.0 to 28.7)	64	10 .0 (6.4 to 13.7)	17.3 (13.1 to 21.4)	23.8 (19.2 to 28.4)	*<0.001*	0.500	0.316	*<0.001*	*<0.001*	*<0.001*
Numerical Rating Scale	57	3.0 (2.2 to 3.8)	2.8 (2.1 to 3.5)	3.0 (2.2 to 3.7)	64	2.7 (1.9 to 3.4)	2.6 (1.9 to 3.2)	2.7 (2.0 to 3.4)	0.816	0.482	0.961	1.000	1.000	1.000
Douleur Neuropathique 4	56	1.8 (1.3 to 2.3)	1.6 (1.2 to 2.1)	1.9 (1.4 to 2.4)	63	1.7 (1.2 to 2.1)	1.5 (1.0 to 1.9)	1.7 (1.2 to 2.2)	0.327	0.514	0.997	0.936	1.000	.305
Modified Ashworth Scale														
Shoulder abduction	58	0.3 (0.1 to 0.5)	0.3 (0.2 to 0.5)	0.4 (0.2 to 0.6)	64	0.4 (0.2 to 0.6)	0.5 (0.3 to 0.6)	0.3 (0.1 to 0.5)	0.589	0.652	0.253	0.829	1.000	1.000
Shoulder intrarotation	58	0.4 (0.2 to 0.6)	0.4 (0.2 to 0.6)	0.5 (0.3 to 0.7)	64	0.5 (0.3 to 0.7)	0.5 (0.3 to 0.7)	0.5 (0.3 to 0.7)	0.776	0.544	0.573	1.000	1.000	1.000
Elbow	58	0.6 (0.3 to 0.8)	0.6 (0.4 to 0.9)	0.8 (0.6 to 1.1)	64	0.5 (0.3 to 0.7)	0.8 (0.5 to 1.0)	0.9 (0.6 to 1.1)	*<0.001*	0.715	0.615	0.085	*0.001*	0.081
Wrist	58	0.5 (0.3 to 0.7)	0.6 (0.3 to 0.8)	0.5 (0.3 to 0.7)	64	0.4 (0.2 to 0.6)	0.5 (0.3 to 0.7)	0.6 (0.4 to 0.8)	0.544	0.824	0.321	1.000	0.931	1.000
SF36—Physical Composite Score	55	29.0 (27.0 to 31.1)	30.8 (28.9 to 32.7)	32.3 (29.9 to 34.6)	61	28.3 (26.4 to 30.2)	29.5 (27.7 to 31.3)	33.0 (30.8 to 35.2)	*<0.001*	0.736	0.329	*0.035*	*<0.001*	*0.001*
SF36—Mental Composite Score	55	42.5 (39.4 to 45.5)	46.3 (43.0 to 49.5)	46.8 (43.7 to 49.8)	61	40.7 (37.8 to 43.6)	45.7 (42.7 to 48.8)	46.8 (43.9 to 49.7)	*<0.001*	0.667	0.684	*<0.001*	*<0.001*	1.000

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; SF36, 36-item Short Form Health Survey.
[a]Values in *italics* indicate a statistically significant difference ($P < 0.05$).

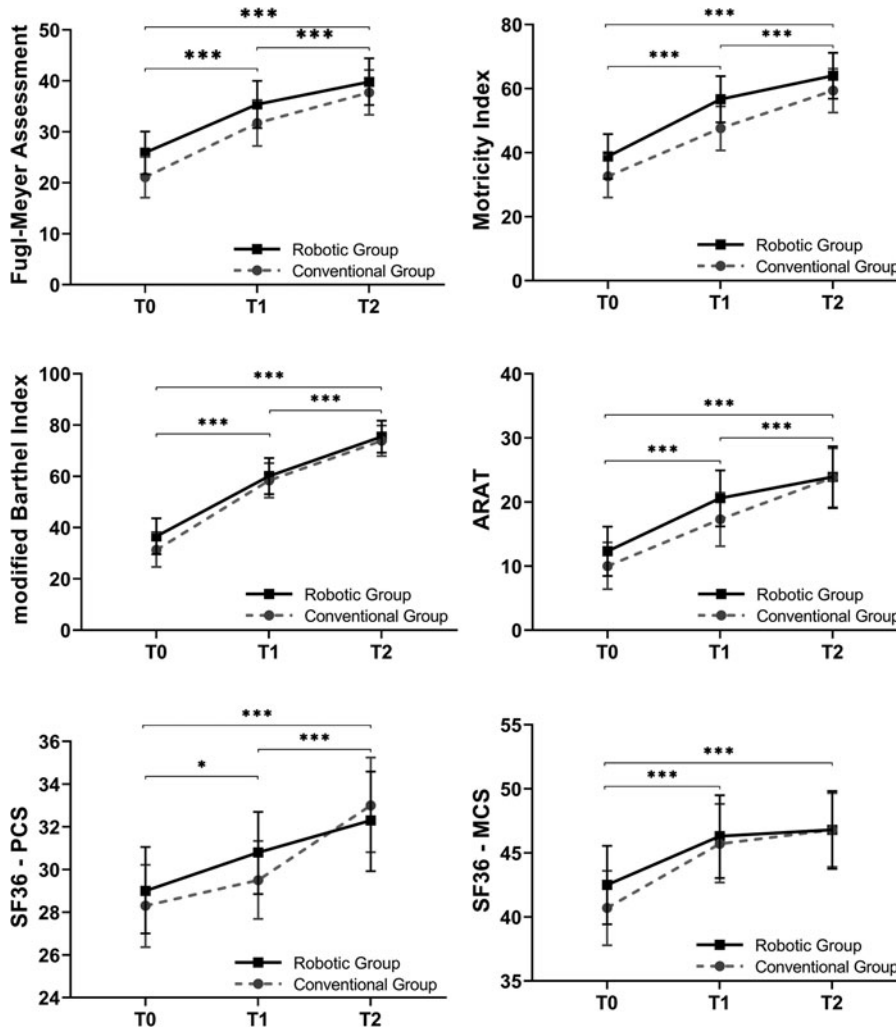

Figure 3. Secondary analysis: evolution of *motor functions* (Fugl-Meyer and Motricity Index), *activities* (modified Barthel Index and Action Research Arm Test) and *participation* (PCS, MCS, and SF36), for the 2 groups, separately. The time points are the baseline (T0), the end of the treatment (T1), and the follow-up at 3 months after the end of the treatment (T2), with error bars representing 95% CI. The interaction factor *time*×*group* was never significant. With respect to the main effect *time*, the asterisks indicate the statistical significance of the post hoc analysis (*$P < 0.05$; ***$P < 0.001$). CI, confidence interval; MCS, Mental Composite Score; PCS, Physical Composite Score; SF36, 36-item Short Form Health Survey.

in the global recovery of stroke survivors, not only for the UL motor function, but also for activities and participation. However, further studies should be focused on the identification of factors associated with responsiveness and recovery potential, and on the identification of the duration of progressive recovery up to a steady state.

With respect to the possible predictors of recovery, we identified 2 variables that were correlated with the recovery (ie, the baseline value of the FMA and subject age). It is well known that functional score at time of admission is correlated with functional outcome,[51] but the relationship between the admission score and the improvement on discharge is not clear. Recent studies have suggested that this relationship is very strong; according to the so-called proportional recovery rule, most stroke survivors recover a fixed proportion of lost UL function (about 70% of the maximal recovery potential). Several studies have supported this hypothesis, using the FMA scale to assess UL motor impairment within 2 weeks of stroke onset ("baseline"), and then again either 3 or 6 months after stroke.[52-56] Our data support the hypothesis that the baseline impairment is one of the most important predictors of recovery after rehabilitation; however, since our baseline data refer to a time since stroke ranging from 2 weeks to 6 months, we can neither confirm nor refute this rule. In addition, it is worth noting that we found meaningful improvements in subjects who had substantial impairment at baseline, and therefore other variables should be considered. To increase accuracy in the prediction of poststroke motor recovery and outcomes, some authors are currently investigating the use of the combinations of measures and biomarkers[57] that could be useful in clinical practice to tailor the therapy content and increase rehabilitation efficiency,[58] but further confirmatory studies are needed.

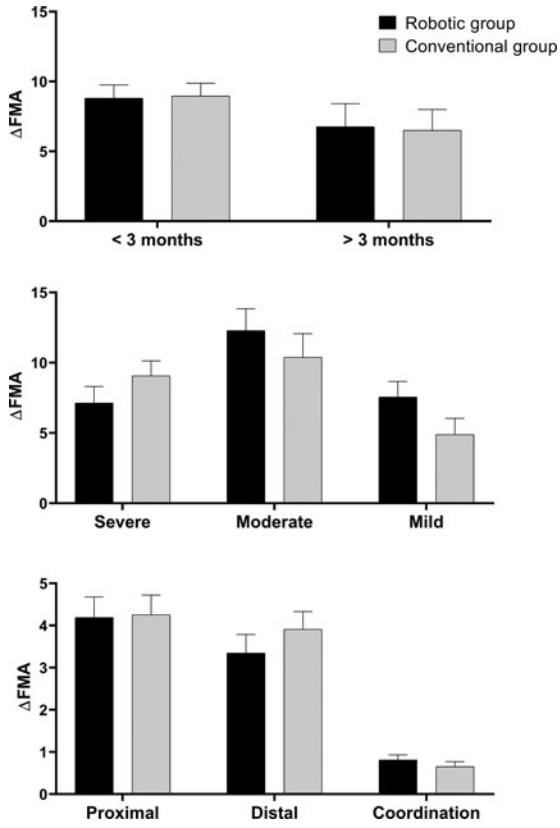

Figure 4. Secondary analysis: comparison of the changes from baseline of the FMA in the 2 groups (robotic vs conventional), considering: subjects with a time since stroke higher or lower than 3 months (top); subjects with an impairment at baseline *severe* (FMA: 0-28), *moderate* (FMA: 29-42), or *mild* (FMA: 43-58) (middle); *proximal, distal,* and the *coordination* subscores of the FMA separately (bottom). All the differences were not significant. FMA, Fugl-Meyer Assessment.

Because of the complexity of the UL, and considering the robotic devices that are currently commercially available, we believed that a set of robotic devices was needed to treat the entire UL (from the shoulder to the hand). In fact, each device of the selected set acts on a different joint and/or on a different plane to allow the motor rehabilitation of the entire UL. The use of 4 devices could be considered a limitation, but the study was designed to compare 2 different approaches that allow treating the UL in its entirety. Used alone, none of the available robots is capable of treating the entire UL, as conventional therapy does. Therefore, it would be desirable to develop new robotic devices capable of treating the UL in a more comprehensive way.

We emphasize that the protocol we used represents the implementation of a new organizational model: in the RG, 1 therapist treated 3 subjects at once, while in the CG, each therapist treated 1 subject at a time. In previous studies similar organizational models were evaluated showing their efficiency in reducing personnel resource allocation.[15,21,59] In our opinion, the added value of the current study is to have compared conventional and robotic therapy, providing a similar amount of time for practice, but reducing personnel resources. This was realized by an organizational model of delivering robotic therapy, which supported its clinical applicability as well as its efficacy. An economically sustainable robotic therapy is crucial to promote the diffusion of this intervention by reducing the additional costs of robotic devices. In the same way, this model could promote adequate UL treatment in countries with a shortage of physical or occupational therapists.[15]

Limitations

The limitations of this study are the high percentage of subjects who did not return for the follow-up, which may lead to the absence of differences between the 2 groups. Likewise, there was a lack of long-term follow-up, to detect the time after which the UL recovery can be considered complete. There was also the lack of a rigid standardization of the intervention implemented in the conventional therapy group, which included some techniques for which there is limited evidence of efficacy. We also did not employ biomarkers of corticomotor function or structure to select subjects for inclusion, which may have contributed to failure to identify between-groups differences. It is possible that assessment of the secondary outcomes was not fully masked, as the therapists completing the assessment were employees of the participating centers. Finally, our study lacked a cost/effectiveness analysis to compare differences related to device and personnel costs.

CONCLUSIONS

In persons with subacute stroke, equivalent amounts of robotic treatment (using a set of 4 devices) and conventional

Table 4. Secondary Analysis (Predictors of Recovery)

Variable	B	Standard Error	*P*	Odds Ratio (95% CI)
Age	− 0.030	0.015	*0.0482*[a]	0.97 (0.94 to 1.00)
Days from index stroke to enrollment	− 0.001	0.004	0.8241	1.00 (0.99 to 1.01)
Baseline impairment (FMA_{T0})	0.026	0.010	*0.0120*	1.03 (1.01 to 1.05)
Affected side = right	− 0.084	0.313	0.7888	0.92 (0.50 to 1.70)
Index stroke type = ischemic	− 0.013	0.378	0.9729	0.99 (0.47 to 2.07)
Group = robotic	0.206	0.316	0.5134	1.23 (0.66 to 2.28)
Constant	2.006			

Abbreviation: CI, confidence interval.
[a]Values in italics indicate statistical significance ($P < 0.05$).

therapy significantly improved UL motor function, activities, and participation to the same extent. Baseline function and age were significant predictors of outcome. The use of robotic devices for therapy delivery allowed the use of a new personnel organizational model; future studies to assess relative cost-effectiveness of robotic therapy delivered using this model are warranted.

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