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Three-dimensional, task-specific robot therapy of the arm: a multicenter randomized clinical trial in stroke patients

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Abstract

Background: Arm hemiparesis, secondary to stroke, is common and disabling. The robot ARMin, which is designed for neurorehabilitation of the arm, allows for task-specific training in a 3-dimensional workspace. The authors assessed whether ARMin reduces impairment and enhances arm motor function of the paretic arm more effectively than conventional therapy. **Methods:** Using a prospective, multicenter (four centers in Switzerland), controlled, parallel-group, single-blind (examiner-blind) demonstration-of-concept study (phase II/stage 3), chronic (more than six months) post-stroke subjects with moderate to severe impairment of an arm, received either neurorehabilitative therapy with ARMin or conventional therapy comprising physical or occupational therapy. The therapy in both groups was given three times per week for eight weeks resulting in 24 therapy sessions on the whole. Each session lasted one hour. A battery of assessments was performed at five time points (t0: before therapy, t1: after four weeks of therapy, t2: at the end of therapy (after 8 weeks), t3: at 16 weeks follow-up, and t4 at 34 weeks follow-up). Primary outcome for evaluating motor function was the change in the impairment-based test, FMA-UE (Fugl-Meyer Assessment of the upper extremity motor function) over the course of the study. **Results:** Out of 77 subjects, 73 completed the study; among them, 38 were enrolled to robotic therapy with ARMin and 35 to conventional therapy. Robotic training of the affected arm with ARMin was found to be more effective than conventional therapy in terms of motor function (FMA-UE: $F = 4{\cdot}1$, $p = 0{\cdot}041$, mean difference: 0·78 points, confidence interval [0·03 - 1·53]). No major adverse events related to the study occurred.

Interpretation: Neurorehabilitative therapy using task-oriented training with an exoskeleton robot can enhance improvement of the paretic arm even in the chronic state after stroke reducing arm impairment more effectively than conventional therapy. However, superiority is based on small

absolute differences and weak significance which leave the clinical relevance and evidence in question. Therapy was shown to be safe.

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Keywords: robotics, exoskeleton, upper limb, arm training, hemiparesis, task-oriented training, neurorehabilitation, stroke, randomized clinical trial

Introduction

Despite preventive measures, stroke remains a leading cause of permanent disability around the world [4]. On average, every 40 seconds a subject in the U.S. suffers a stroke [5], and 30% to 66% of the survivors suffer from long-term loss of arm function [6]. As conventional therapeutic approaches for functional rehabilitation after stroke show limited effectiveness [7], robotic approaches are increasingly being subjected to scientific scrutiny [8]. A Cochrane meta-analysis [9] compared the efficacy of robotic devices to other therapeutic interventions in treating motor dysfunction after stroke. Results show that paretic arm function and activities of daily living (ADL) may improve with these devices, but not arm muscle strength. It is of debate whether dose accounts for the effectiveness of robot-assisted therapy [10-12]. Robotic devices allow for further modes of therapy that cannot be accomplished with conventional therapy methods, such as adaptive training [13], or highly repetitive, complex movements [14]. The devices that were tested in the Cochrane meta-analysis [9] mainly support single joints or allow for planar movements only [12, 15]. The exoskeleton robot ARMin (Figure 1, [16]) features a large range of motions in the 3-dimensional space; it provides intensive and task-specific training strategies for the arm which have been identified to be particularly effective in promoting motor function [17-20]. With seven degrees of freedom, ARMin supports the physiological movements of the shoulder and arm, as well as opening and closing of the hand. A teach-and-repeat procedure is implemented, where the therapist can mobilize the patient's arm on an arbitrary, patient-individual trajectory, while the robot actively compensates friction and gravity [16]. A battery of games and activities of daily living (ADL) can be practiced in a virtual reality environment. They include ball games, a labyrinth game and different kitchen activities [14]. Audiovisual cues and online information about performance are provided to increase motivation. Within the ADL tasks and games, the patient moves his arm in a virtual tunnel (patient-cooperative

path controller [14]). Parameters such as difficulty, speed, tunnel width, and gravitational and movement assistances are adjusted by the therapist.

The main question addressed in the present study is whether robotic training of the affected arm with ARMin reduces motor impairment with respect to arm and hand function more effectively than conventional therapy. As primary outcome, changes in motor function over the course of the study were measured by means of the upper-limb portion of the Fugl-Meyer assessment (FMA-UE). Furthermore, we investigated whether robotic therapy with ARMin had long-term effects on impairment, activity and participation, and which subpopulations (stratified by time gap since stroke, severity, age, hand dominance) benefit most from the interventions.

Methods

Study design and participants

This study was a prospective, multicenter, parallel-group designed trial. Randomization was performed by an independent person not involved in the study. All assessors (N=5) were blinded for treatment allocation. It was designed to act as a demonstration of concept trial testing the safety and developing preliminary efficacy data (phase II/stage 3, according to Dobkin [21]). Participants after first-ever cerebrovascular accident (CVA) were randomly assigned to robotic or conventional therapy. Four clinical centers in Switzerland (Uniklinik Balgrist UKB, Reha Rheinfelden RRh, Zentrum für Ambulante Rehabilitation Zürich ZAR, Zürcher Höhenklinik Wald ZHW) were involved in recruitment and therapy. ZHW and RRh are neurorehabilitation centers in the agglomeration of Zurich and Basel with a catchment area of approximately 1.2 million individuals. Through inpatient and outpatient facilities, each center treats between 300 and 600 subjects after CVA annually. ZAR is an outpatient clinic for neurorehabilitation situated in Zurich with more than 100 subjects after CVA per year treated. UKB is the clinical partner for technical development of the ARMin robot and situated in Zurich. All the participating centers are experienced in clinical research projects.

Subjects were recruited through the centers and media during the course of the study. They were considered eligible if they were diagnosed with a single CVA in the chronic state (minimum six months) with moderate to severe arm paresis (8 to 38 points of the FMA-UE). To approve chronic state post-stroke, the FMA-UE was repeated after three to four weeks (t0) and a difference of up to 3 points was accepted for inclusion (see Table 1 for further eligibility criteria). Written informed consent was obtained from each participant prior to enrollment.

Because of difficulties in enrolling the intended number of subjects, the study was prolonged for 17 months and the eligibility criteria were widened 19 months after start of the study, as follows: The criterion “ischemic stroke” was extended to “CVA”; the exclusion criterion “epilepsy” was discarded and the age restriction changed from “18 to 80 years” to “minimum 18 years”. Subjects who had not been originally considered or rejected, due to these eligibility criteria, were contacted and testing for eligibility was offered. Because of recruitment difficulties at one center, five allocation envelopes were transferred from there to another center to treat five additional participants at the latter.

Procedures

Therapy of both groups (robotic and conventional therapy) was applied in the centers for a period of eight weeks, three times weekly (total 24 sessions). Only one session per day was scheduled. Missed sessions (up to four) could be rescheduled if training duration did not exceed nine weeks. Minimal time for therapy (excluding time for preparation, diagnostics, documentation etc.) for both groups was 45 minutes.

During the robotic therapy with ARMin, each of the three therapy modes (mobilization, games, and ADL training) had to be performed for a minimum of ten minutes each. The control group received “conventional therapy”: the term denotes the common neurorehabilitation treatment applied to stroke patients in outpatient facilities, namely occupational therapy or physiotherapy. Therapists

were asked to perform a regular therapy usually including mobilization, games and/or ADL. Only restriction was not to use automated technical devices that might be available in therapy settings.

The same occupational and physical therapists conducted both training forms (robotic and conventional therapy) and were assigned to the individual participant prior to the allocation of therapy type. Therapists had more than four years of professional experience. At two centers an occupational therapist, at one center a physical therapist, and at one center a physical and an occupational therapist were involved, but each participant was treated by the same person (each with a substitute). Each therapist received several hours of teaching in robotic therapy by an instructed therapist and the responsible engineer (one-to-one-training, observation at therapies, supervised training).

Primary outcome was the change in FMA-UE score. The motor impairment test involves 33 items, which assess voluntary movement, reflex activity, grasp, and coordination on an ordinal scale (0-1-2), with a total score of 0 (“no function”) to 66 points (“normal function”) [22]. The threshold for the minimal clinically important difference (MCID) in chronic subjects with minimal to moderate impairment after stroke is about 5 points (4.25 to 7.25 points [23]) and the minimal detectable change (MDC95) is 8% or 5.2 points [24, 25].

Secondary outcome measures included the Wolf Motor Function test (WMFT), a disability-based test of 15 tasks, that assesses the quality ($WMFT_f$: 0 = “does not attempt with the involved arm” to 5 = “affected arm does participate; movement appears to be normal”) and time ($WMFT_t$: max. 120 seconds) of task performance [26, 27]. Six tasks relate to joint-segment movements and nine tasks to integrative functional movements. In addition, grip strength is measured with a handheld dynamometer (Jamar). Following were the other secondary outcome measures: i) the quality of movement section of the Motor Activity Log (MAL-QOM,[28]), a semistructured interview with 30 questions that evaluate the use of the paretic arm and hand during ADL with a rank order scale (0-5),

ii) the Stroke Impact Scale version 2.0 (SIS, [29]), a self-report questionnaire composed of 60 items that investigate changes in nine domains, comprising impairment, disability, and handicap (SIS: total score; physical domain SIS_{pd}: combination of the four domains strength, hand function, mobility and ADL), iii) the Goal Attainment Scale (GAS, [30]), a measure of goals that could be achieved with the intervention (two goals were defined by the therapist together with the patient in the first therapy session; the achievement at the last session was measured on a 5-point scale ranging from -2 to +2 and then averaged), iv) the modified Ashworth Scale (mAS, [31]), a test of resistance to passive joint movement (we averaged the mAS values from the following nine single joint movements: flexion and extension of elbow, wrist, finger, thumb; and flexion of the shoulder), and v) mean strength measured by ARMin (the subject's arm is brought to predefined positions and the subject applies maximal, voluntary, isometric torques in directions of shoulder abduction/adduction/anteversion/retroversion and elbow flexion/extension; peak torques are derived from the measured counter-steering motor currents, and the mean strength in Newtonmeter calculated).

Evaluators included a physician in training and occupational therapists or physiotherapists, all blinded to group assignment. They were first instructed by a therapist at ETH Zurich to ensure standardization. Instruction included a theoretical and practical education program and supervised practice on subjects. Evaluators performed battery testing at six time-points: three to four weeks before assignment (tm1), immediately before therapy (t0), 4-weeks interim therapy (t1), at the end of 8-weeks therapy (t2), and at 16-week (t3) and 34-week follow-ups (t4) (see Figure 1). Only those subjects who fulfilled all the eligibility criteria at t0 were included.

Data management and monitoring, and administration were controlled by the study coordinator. The principal investigators of each of the clinical centers approved all decisions and met annually to assure conductance according to the protocol. The study procedures were approved by the

150 respective institutional review boards of each participating center (Cantonal Ethical Committees).
151 The study was registered on ClinicalTrials.gov (ClinicalTrials.gov identifier, NCT00719433).

152

153 ***Randomization and Masking***

154 We used a center-stratified randomization procedure with one block for each center and a
155 proportion of 1:1 for robotic to conventional therapy. A computer-generated list of random numbers
156 [32] which pair both a unique sequential number and the treatment type (robotic/conventional) was
157 used. Pairs were sealed in tamper-evident envelopes by the study coordinator. Subjects drew lots
158 which were presented by a person not involved in testing. The assignment to an occupational or
159 physiotherapist was not randomized but determined by the available clinical staff on site. Evaluators
160 were blinded to treatment allocation and the clinical tests FMA-UE and WMFT were video-taped for
161 later control.

162 Clinical centers and group assignment were coded during data processing. In this way, we aimed to
163 avoid bias in reporting, data processing and data analysis. For each participant, all recorded data
164 were cross-checked by a study nurse not involved in data collection.

165

166 Statistical Analysis

167 The calculation of the sample size was based on the data of the FMA-UE of a comparable study [33]
168 that assessed the effects of robot-assisted training and conventional therapy in 27 chronic stroke
169 patients. After two months of training, an average improvement in the FMA-UE score of 4.7 and 3.1
170 points, respectively, was found. The largest standard deviation (SD) was 2.5 points. Assuming $\alpha < 0.05$
171 when tested two-tailed and a requested power of 80% a target sample size of 80 participants was

needed for the trial [34]. Expecting a drop out of 10%, we chose a sample size of 44 participants for each group, which resulted in a final target size of 88.

A significance level of 0.05 was defined for all the analyses. A repeated measures linear mixed model was used to assess the effect of treatment over the entire course of the study for each of the outcome measures. In each model, group (ARMin, control) was used as the between-subjects factor, baseline function (baseline value at t0), and time gap since stroke (in months) as covariates, and center (centers 1, 2, 3, 4) as random effect. The model assumptions were checked using Tukey-Anscombe residual plots and quantile-quantile (QQ) plots. The secondary outcome GAS was only assessed at a single time point (t2). As such, a univariate ANOVA with the same model term structure was used. All calculations were performed using IBM SPSS 20.

During the process of data analysis, we decided to perform hypothesis generating post-hoc subgroup analyses. The subjects were divided based on median splits for “time gap since stroke”, “age”, “hand dominance”, and “severity” (FMA-UE at t0) in the linear mixed model.

According to “intention-to-treat” analysis, all assigned participants were analyzed after their initial entry check regardless of a) their adherence with the entry criteria b) the treatment they received and c) a deviation from the protocol [35]. A modified application of the intention-to-treat was followed, meaning that subjects were only included when outcome data from follow-up assessments were available for the randomized subjects. For missing data, the last observation was carried forward or, if no former observation was applicable, the next observation carried backward [36].

Role of the funding source

The corresponding author has final responsibility for the decision to submit for publication. All authors had full access to all of the data in the study.

Funding sources were the Swiss National Science Foundation and the Bangerter-Rhyner Foundation. They were neither involved in the study design nor in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Results

Between May 2009 and September 2012, 145 subjects (out of 275 subjects screened) were clinically tested for eligibility. The target number of 88 participants was not reached. Seventy-seven subjects were eligible and agreed to participate (Figure 2). Subjects were randomly assigned to either robotic (n = 39) or conventional (n = 38) therapy. The dropout rate was 5%: two participants rejected participation when they were allocated to conventional therapy, one participant developed epileptic seizures during the course of the study and one participant had an accident not related to the study. *S*eventy-three subjects completed the study with a total of 38 and 35 in the ARMin and the control group, respectively: 13 and 12 in center 1; 11 and 8 in center 2; 5 and 6 in center 3; 9 and 9 in center 4; one subject was included in the analysis although he had stopped therapy midway due to medical reasons unrelated to the study, but finished tests ("intention-to-treat"). Eight out of 365 assessments (73 times five assessments) were missed. Three subjects had fewer than 24 therapy sessions (20, 21 and 23 therapies, respectively). Two subjects had to be excluded because they had more than 3 points difference in the FMA-UE between the tests m1 and t0. Three subjects were included by the evaluators although they exceeded this number (4, 4, and 5 points, respectively) to fulfill the "intention-to-treat" [35]. The subjects' baseline characteristics are summarized in Table 2. Average therapy time per session was 46 minutes (SD ±4.0) in the robotic group and 48 minutes (SD±3.7) in the control group.

Safety

The participants experienced no serious side effects from the study. Two subjects had minor events relating to the robotic device during the testing procedure: the skin of their arm was bruised leading to flushes of about 1 cm diameter. The device was padded and adjusted, to avoid recurrence of such events. One subject from the ARMin group reported mild shoulder pain; the therapy was interrupted for three sessions and then resumed without further adverse events.

Effects of Therapy

Primary Outcome

In the FMA-UE, differences between the two treatment groups over the course of the study were significant (FMA-UE: F = 4·1, p = 0·041, mean difference: 0·78 points, confidence interval, CI [0·03 - 1·53], Figure 3). Thirteen out of 38 subjects (34%) in the ARMin group and 9 out of 35 subjects (26%) in the control group gained 5 or more points during therapy (t0 to t2, “responders”).

Secondary Outcomes

Linear mixed models revealed significantly lower gains in mean strength in the ARMin group than in the control group (F = 5·8, p = 0·017, mean difference: 1·29 Nm, CI [- 2·34 to -0·23], see webappendix). Among the remaining secondary outcomes (SIS, SIS_{pd}, WMFTt, WMFTf, MAL(QOM), GAS, mAS, grip strength) no significant differences between the treatment groups could be revealed (Table 3). For mean strength, normality of residuals in the QQ plot was partly violated and could not be achieved by variable transformation.

Subgroup analysis

When subjects were stratified (applying the median of the respective attributes) according to i) time gap since stroke (< 27 months vs. ≥ 27 months), ii) age (<59 years vs. ≥59 years) or iii) hand dominance (dominant hand affected vs. non-dominant) the outcome was not conclusive regarding changes in motor function. Splitting by iv) severity (<19 points vs. ≥19 points in baseline FMA at t0), a tendency in favor of ARMin over the course of the study could be observed in the more severely affected subjects ($F = 17.36$, $p < 0{\cdot}001$, mean difference: 1·91 points, CI [1·00 to 2·82], see webappendix).

Discussion

The results of this study confirm that robotic training with ARMin reduces motor impairment with respect to arm and hand function more effectively than conventional therapy. This superiority is based on small absolute differences (0·78 points in the FMA-UE) and a weak significance ($p = {\cdot}041$) which leave the clinical relevance and evidence in question.

Noteworthy were the gains with robotic therapy in severely affected subjects: it seems that they particularly benefitted from ARMin therapy with a mean difference of 1·91 points in the FMA-UE between the two groups (see also webappendix). These results were acquired in a sub-group analysis. Further studies on severely affected subjects should be conducted before definite conclusions can be drawn.

Intensity of training might be an important factor, though not the only one to favor ARMin. With the robot, task-oriented activities can be trained in 3D-workspace that might be hard to reach during conventional therapy of a severely affected arm; and the patient-cooperative control strategy facilitates the accomplishment of a subject-initiated task.

Although the mean gains in the ARMin group averaged 3·25 points in the FMA-UE and were superior to conventional therapy (2·47 points), these changes do not represent clinical relevance with respect to the MCID (about 5 points [23]). Although this MCID was established in subjects with minimal to moderate impairment and does not fully apply to the present target group of moderately to severely affected subjects, it illustrates the challenge to achieve meaningful improvements within the limitations of a clinical study. About one third of the subjects in the ARMin group achieved meaningful gains (increase in FMA-UE ≥5 points), against one fourth in the control group. Probably, not all the subjects tapped full potential with only eight weeks of therapy. Although most gains in the robotic group occurred in the first four weeks, subjects improved during the second half of therapy and might have continued so with longer training. A pilot study on robotics had shown that durable and intense treatment facilitated an incremental progression that was necessary for severely affected individuals [36].

The results of follow-up tests revealed convergence of both groups, indicating that the robotic group remained fairly stable after therapy while the conventional group continued to improve slightly during the follow-up phases and reached a result similar to that of the robotic group after four weeks therapy (Figure 3). The robotic group gained motor function faster but could not fully consolidate the achievements when the therapy ceased. The results raise the question as to whether the participants in the conventional therapy group learned something that was not reflected in the tests during and immediately after therapy, but useful for further progression during the follow-up. It might be explained by the higher strength gains in the conventional group (see webappendix) which might have enhanced the use of the affected arm in daily life. The present results are in accordance with the findings of the Cochrane meta-analysis [9]: robotic devices may improve paretic arm function, but not arm muscle strength. In the case of ARMin, the parameters for the path assistance might have been chosen too supportive, in this way restraining strength training. Further research should

focus on ascertaining if specific strength tasks have to be added to robot therapy to enhance improvement [37].

Beside of mean strength, no other secondary outcome measure showed significant differences in favor of either of the two treatments.

Due to the nature of an interventional study, participants and therapists are not blinded to group assignment which might erode the validity of the results of a trial. Participants are prone to favor the robotic therapy. In addition, a robotic treatment group might benefit from the incentive of a new therapy. On the other hand, therapists might perceive the robot as a competitor either affecting the way they perform the robotic training or resulting in contamination of the conventional therapy (e.g. by increasing repetition).

Several limitations of the study can affect the validity of the results. The eligibility criteria are potentially problematic. We restricted participation in this study to participants in the chronic state to assure that improvement is due to the therapy applied and not to spontaneous recovery. However, this runs the risk that compensation rather than true recovery is the primary mechanism of functional gains [33]. The intended number of 80 participants could not be reached. The achieved sample size of 73 participants was sufficient to detect significant differences for FMA-UE and mean strength. While the FMA-UE did fulfill the model assumptions, some deviation from normality was observed for mean strength. Results for mean strength should hence be treated with caution.

More than 70% of participants were engaged in regular rehabilitation (occupational and physical therapies) before entering the study, with an average of more than three sessions weekly. Thus, the full potential might have been already exploited and a therapeutic plateau reached in both groups.

In conclusion, we found that neurorehabilitative therapy with task-oriented training, using an exoskeleton robot is safe and can enhance motor recovery of the paretic arm in moderate to severely affected subjects even in the chronic state after stroke. It reduced arm motor impairment more

effectively than did conventional therapy. The mean difference in the FMA-UE was statistically significant but small and is of little clinical relevance for the individual. Both groups gained about three points in the FMA-UE over the course of the study (Figure 3). Plotting the means over time implies that recovery is faster with robot-assisted therapy than with conventional therapy. The ARMin group performed better particularly when we restrict our attention to the severely affected study participants, but these results of post-hoc subgroup-analysis with split sample sizes need caution and further investigation.

That the potential for recovery persists even months after stroke has been verified by several studies [38, 39]. The application of robotic therapy might guide subjects after stroke beyond what is possible with current practice alone.

Formatiert: Englisch (USA)

Competing interests

V. Klamroth-Marganska reports grants from Swiss National Science Foundation and from Bangerter-Rhyner Foundation, during the conduct of the study. In addition, R. Riener and T. Nef are inventors of the patents “System for arm therapy“(WO2008EP08556 20081010) and "System und Verfahren für die kooperative Armtherapie sowie Rotationsmodul dafür” (WO2006058442). ETH Zurich signed a license contract with Hocoma AG (Volketswil, Switzerland), a company which develops and sells rehabilitation robotic devices for treatment of neurological patients. There are no conflicts of interest for J. Blanco, K. Campen, A. Curt, V. Dietz, T. Ettlin, M. Felder, B. Fellinghauer, M. Guidali, A. Kollmar, A. Luft and C. Schuster-Amft.

Authors’ contributions

V. Klamroth-Marganska participated in the following aspects of the study: concept and design, coordination, data analysis and interpretation, and manuscript drafting.

J. Blanco, K. Campen, T. Ettlin, M. Felder and C. Schuster-Amft participated in the study design and coordination, besides manuscript revision.

A. Curt contributed to the design and supervision of the study, data interpretation and manuscript revision.

V. Dietz participated in concept and design of the study, temporary supervision of study, and in data interpretation and manuscript revision.

B. Fellinghauer and W. Stahel planned the statistical procedures and performed parts of the statistical analyses.

M. Guidali contributed to the study design, coordinated parts of the study, helped in data acquisition and manuscript revision.

A. Kollmar contributed to the study design and helped in data acquisition and manuscript revision.

A. Luft contributed to the study design and was involved in data interpretation and manuscript revision.

T. Nef, together with R. Riener, initiated and planned the study concept and design and revised the manuscript.

R. Riener headed the project and, together with T. Nef, designed, initiated and planned the study, besides being involved in data interpretation, and drafting and revising the manuscript.

All authors have read the final manuscript and gave their approval for its publication.

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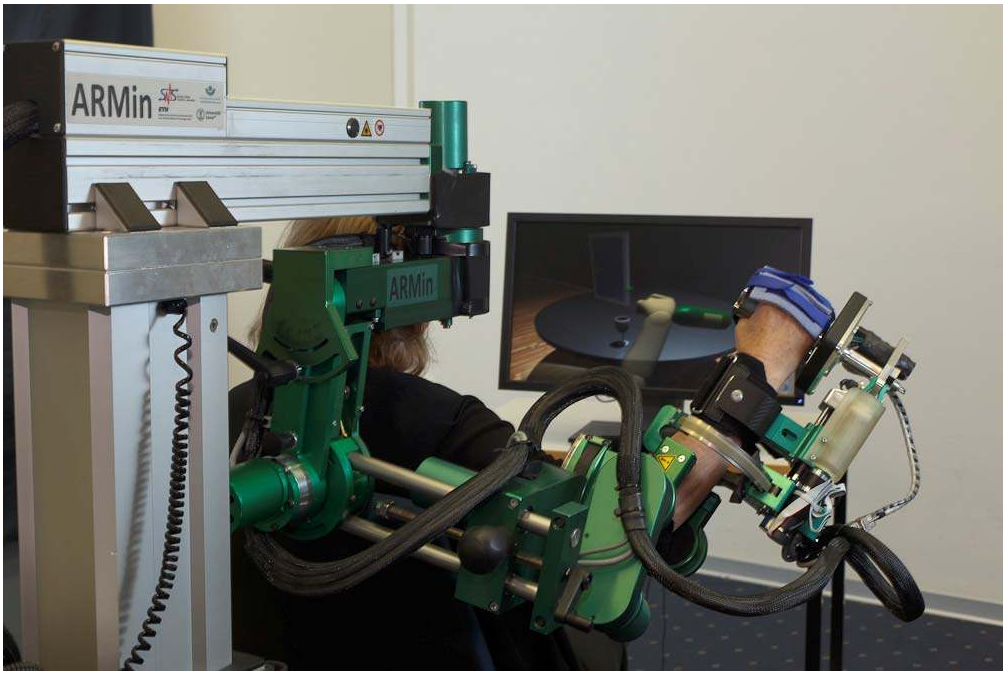

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468 **Figure 1** Subject performing task-oriented training (filling a glass) with ARMin

469 **Table 1 Eligibility criteria for participation in the study**

Diagnosis of a single, first ever cerebrovascular accident (CVA) verified by brain imaging (magnetic resonance imaging [MRI] or computer tomography [CT])
Chronic stage after stroke (minimum six months)
Moderate to severe arm paresis, as indicated by a score of 8 to 38 out of the maximum 66 points in the FMA-UE

Minimum age 18 years
Stable recovery stage
Able to sit in a chair without any additional support and without leaning on the back rest
Passive range of motion (pROM) in the shoulder: anteversion/retroversion 80˚/0˚/20˚, abduction/adduction 60˚/0˚/10˚, inner and outer rotation 20˚/0˚/20˚; in the elbow: flexion/extension 100˚/40˚/40˚
No excessive spasticity of the affected arm (modified Ashworth Scale mAS ≤ 3 out of 0-5)
No serious medical or psychiatric illness
No participation in any clinical investigation within four weeks prior to the start of this study
No participation in any therapeutic treatment (outside therapy) performed with the paretic arm during the therapy phase of the study
No anticipated need for any major surgery during the study
No pregnancy or breast feeding (for women subjects); no orthopedic, rheumatologic or other disease restricting movements of the paretic upper extremity
No shoulder subluxation (palpatory < 2 fingers)
No skin ulcerations at the paretic arm
Ability to communicate effectively with the examiner such that the validity of the patient's data could not be compromised
No cybersickness
No pace-maker or other implanted electric devices
Body weight lower than 120kg
No serious cognitive defects or aphasia preventing the performance of the ARMin treatment

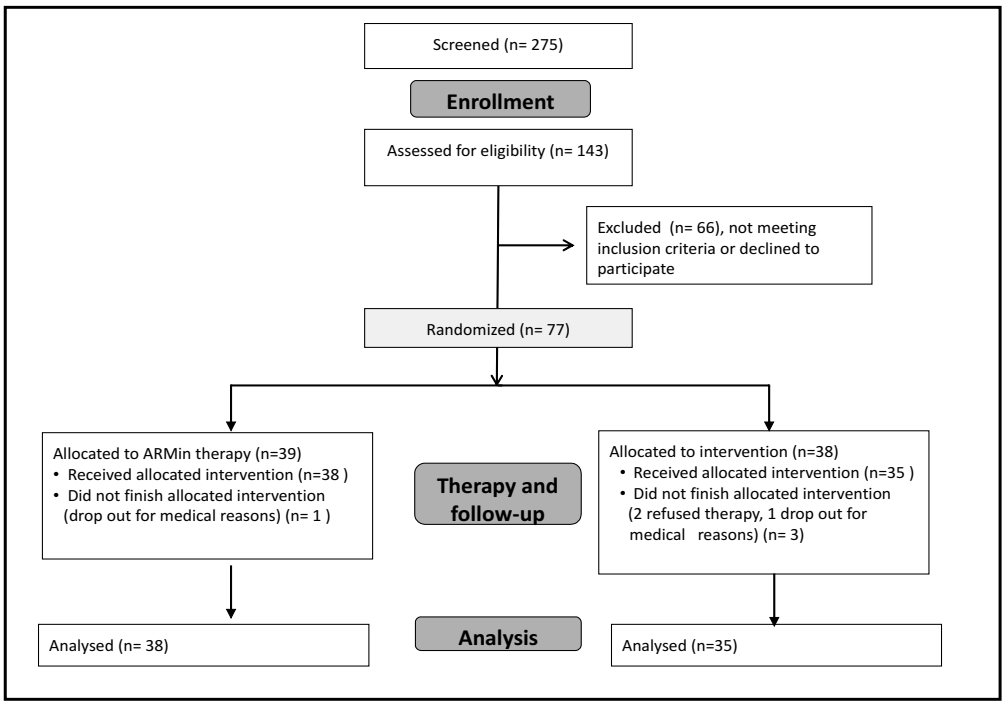
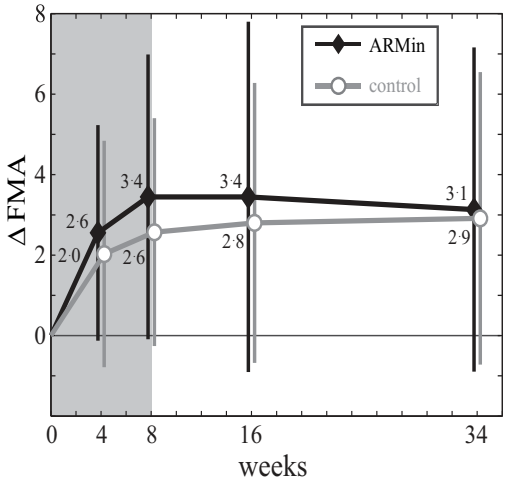


Figure 2 Flow diagram of study enrollment and completion

Table 2 **Baseline characteristics of participating subjects. FMA-UE: Fugl-Meyer Assessment (upper extremity motor function); WMFT: Wolf Motor Function Test: MAL-QOM: Motor Activity Log, quality of movement; SIS = Stroke Impact Scale.**

	ARMin		control	
	N	Mean ± SD (min – max)	N	Mean± SD (min – max)
Age in years at therapy	38	55±13 (22 – 75)	35	58± 14 (27 – 76)
Months since stroke	38	52±44 (7 – 171)	35	40± 45 (7 – 168)
Gender				
Female	17		10	
Male	21		25	
N with additional therapy	20		23	
Hours per week	30	1.6±1.7 (0 -6)	34	1.8± 1.8 (0 – 6)
Total therapy hours	30	2.2± 2.2 (0 – 9)	34	2.2±2.1 (0 – 8)
Physiotherapy	30	1.0±1.0 (0 – 3)	34	1.0±0.9 (0 – 3)
Occupational therapy	30	0.7±0.9 (0 – 3)	34	0.8±0.9 (0 – 3)
FMA-UE baseline	38	20.2±7.1 (8 – 36)	35	20.7±8.2 (8 – 37)
WMFT function	38	2.0±0.8 (0.7 – 3.3)	35	2.0±0.6 (0.8 – 3.9)
WMFT time	38	67±23 (22 – 114)	35	65±29 (3 – 112)
MAL-QOM	38	0.8±0.6 (0 – 2.3)	35	0.8±0.6 (0.1 – 2.3)
SIS total	38	64±11 (41 – 83)	35	62±11 (31 – 81)
SIS physical domain	38	53±13 (21 – 81)	35	52±13 (24 – 72)
mAS	38	0.8±0.4 (0.0-1.8)	35	0.6±0.4 (0.0-1.8)
Mean strength (Nm)	38	10±8 (0 – 32)	35	11±7.6 (0 – 29)
Grip strength	38	5.0±4.8 (0 – 19)	35	5.6±4.7 (0 – 18)
FMA-UE baseline ≥19	22	25±5 (19-36)	17	27±6 (19-37)
FMA-UE baseline <19	16	14±3 (8-18)	18	15±3 (8-18)
FMA-UE in subjects with months since stroke <27	21	20.3±6.8 (8-36)	15	21.4±9.7 (9-37)
FMA-UE in subjects with months since stroke <27	17	20.2±7.6 (9-34)	20	20.3±7.1 (8-37)
Age < 59 years	19	45±9.9 (22-56)	16	46±9.4 (27-57)
Age ≥59 years	19	66±5 (59-75)	19	69±5 (59-76)
Months since stroke <27	17	18±6 (7-26)	20	13±6 (7-25)
Months since stroke ≥27	21	80±42 (28-171)	15	76±48 (29-168)
Hand dominance/ impaired side				
Left/left	2		0	
Right/left	17		19	
Right/right	17		15	

Left/right	2		1	
Dominant side affected	19		15	



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477 **Figure 3** Change in FMA-UE as compared to baseline during the course of study - a comparison between
478 conventional (control) and robotic therapy groups (ARMin); Error bars are standard deviations.

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480 **Table 3** F-ratios,significance levels, estimated marginal means, and confidence intervals for primary and
481 secondary outcomes. CI: confidence interval; FMA-UE: Fugl-Meyer Assessment (upper extremity motor
482 function); WMFT: Wolf Motor Function Test: MAL-QOM: Motor Activity Log, quality of movement; SIS = Stroke
483 Impact Scale, mAS = modified Ashworth Scale; GAS = Goal Attainment Scale.

group effect				
	F-ratio	**p value**	**estimated marginal means**	**CI**
FMA-UE	4·2	·041	0·78	0·03 to 1.53
WMFT time	1·4	·173	2·02	-0·90 to 4·93
WMFT function	1·6	·212	-0·37	-0·10 to 0·021
SIS total	3·6	·059	1·42	-0·05 to 2·91
SIS physical domain	0·8	·387	0·76	-0·96 to 2·47

MAL-QOM	·1	·751	0·13	-0·07 to 0·10
mAS	3·0	·083	-0·62	-0·13 to 0·01
GAS	3·23	·077	-0·39	-0·82 to 0·04
Mean strength	5·7	·017	-1·29	-2·34 to - 0·23
Grip strength	1·7	·196	-0·41	-1·04 to 0·21

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Research in context:

We searched Medline (1950 till October 16, 2013) and Google Scholar for articles published in any language with the search terms “stroke”, “robot”, “randomized” or “randomised”, “clinical trial”, “exoskeleton” or “exoskeletal”, “upper limb” or “upper extremity” or “arm”, and “task-oriented”. We obtained 209 articles. After visual inspection we included all RCT’s focusing on upper limb rehabilitation training with a robotic exoskeleton device that allows task-specific training. This inspection resulted in three publications. Two RCT [1, 2] reported about therapy results with the T-WREX system, a passive 5 degree-of-freedom arm orthosis that contains no robotic actuation but offers variable levels of gravity support. One study with an exoskeleton robot (UL-EXO7)[3] reported a RCT, where 15 subjects were randomly assigned to either bilateral UL-EXO7 training, unilateral UL-EXO7 training, or usual care. However, in this publication, only the two robotic training groups were reported but not the control group (usual care).

The search confirmed that no RCT on exoskeleton robots had been published.

Interpretation:

The present RCT study is the first one that compares upper limb rehabilitation training with a robotic exoskeleton device with conventional therapy in chronic post-stroke subjects. The results indicate that robotic training of the affected arm with the ARMin exoskeleton reduces impairment and enhances arm motor function more effectively than conventional therapy.