Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial

Verena Klamroth-Marganska, Javier Blanco, Katrin Campen, Armin Curt, Volker Dietz, Thierry Ettlin, Morena Felder, Bernd Fellinghauer, Marco Guidali, Anja Kollmar, Andreas Luft, Tobias Nef, Corina Schuster-Amft, Werner Stahel, Robert Riener

Summary

Background Arm hemiparesis secondary to stroke is common and disabling. We aimed to assess whether robotic training of an affected arm with ARMin—an exoskeleton robot that allows task-specific training in three dimensions—reduces motor impairment more effectively than does conventional therapy.

Methods In a prospective, multicentre, parallel-group randomised trial, we enrolled patients who had had motor impairment for more than 6 months and moderate-to-severe arm paresis after a cerebrovascular accident who met our eligibility criteria from four centres in Switzerland. Eligible patients were randomly assigned (1:1) to receive robotic or conventional therapy using a centre-stratified randomisation procedure. For both groups, therapy was given for at least 45 min three times a week for 8 weeks (total 24 sessions). The primary outcome was change in score on the arm (upper extremity) section of the Fugl-Meyer assessment (FMA-UE). Assessors tested patients immediately before therapy, after 4 weeks of therapy, at the end of therapy, and 16 weeks and 34 weeks after start of therapy. Assessors were masked to treatment allocation, but patients, therapists, and data analysts were unmasked. Analyses were by modified intention to treat. This study is registered with ClinicalTrials.gov, number NCT00719433.

Findings Between May 4, 2009, and Sept 3, 2012, 143 individuals were tested for eligibility, of whom 77 were eligible and agreed to participate. 38 patients assigned to robotic therapy and 35 assigned to conventional therapy were included in analyses. Patients assigned to robotic therapy had significantly greater improvements in motor function in the affected arm over the course of the study as measured by FMA-UE than did those assigned to conventional therapy (F=4·1, p=0·041; mean difference in score 0·78 points, 95% CI 0·03–1·53). No serious adverse events related to the study occurred.

Interpretation Neurorehabilitation therapy including task-oriented training with an exoskeleton robot can enhance improvement of motor function in a chronically impaired paretic arm after stroke more effectively than conventional therapy. However, the absolute difference between effects of robotic and conventional therapy in our study was small and of weak significance, which leaves the clinical relevance in question.

Funding Swiss National Science Foundation and Bangerter-Rhyner Stiftung.

Introduction

Despite preventive measures, stroke remains a leading cause of permanent disability worldwide.[1] On average, someone in the USA has a stroke every 40 s[2] and 30–66% of the survivors have long-term loss of arm function.[3] Because conventional therapeutic approaches for functional rehabilitation for chronic impairment after stroke have limited effectiveness,[4] robotic approaches are increasingly being investigated.[5]

In a Cochrane meta-analysis,[6] the efficacy of robotic devices was compared with that of other therapeutic interventions for treatment of motor dysfunction after stroke. Results showed that arm function and activities of daily living, but not arm muscle strength, could improve with these devices. Whether intensity of therapy accounts for the effectiveness of robot-assisted therapy is a matter of debate.[7–9] Further modes of therapy that cannot be accomplished with conventional therapy methods—eg, adaptive training[10] or highly repetitive, complex movements[11]—can be achieved with robotic devices.

The devices that were included in the Cochrane meta-analysis[6] mainly support one joint or allow for planar movements only.[9,12] The exoskeleton robot ARMin[13] (figure 1) allows large ranges of motions in three dimensions, and provides intensive and task-specific training strategies for the arm that are particularly effective for promotion of motor function.[14–17] With seven actuated axes (ie, degrees of freedom), ARMin supports the physiological movements of the shoulder and arm, and the opening and closing of the hand. A teach-and-repeat procedure is implemented, whereby the therapist can mobilise the patient's arm on an arbitrary, individual trajectory, while the robot actively compensates for friction and gravity.[13] Various games and activities of daily living can be practised in a virtual reality environment, such as ball games, a labyrinth game, and different kitchen activities.[11] Audiovisual cues and online information about performance are given to the patient to increase motivation. Within the tasks and games, the patient moves his or her arm in a virtual tunnel, in which variables such as difficulty, speed,

Lancet Neurol 2014; 13: 159–66

Published Online December 30, 2013 http://dx.doi.org/10.1016/S1474-4422(13)70305-3

See Comment page 132

Sensory-Motor Systems Lab, Institute of Robotics and Intelligent Systems, Department of Health Sciences and Technology (V Klamroth-Marganska MD, M Guidali PhD, A Kollmar, Prof R Riener PhD)**, and Seminar for Statistics** (B Fellinghauer PhD, W Stahel PhD)**, ETH Zurich, Zurich, Switzerland; Spinal Cord Injury Center, University Hospital Balgrist** (V Klamroth-Marganska, Prof A Curt MD, Prof V Dietz MD, M Guidali, A Kollmar, Prof R Riener)**, and Clinical Neurorehabilitation, Department of Neurology** (Prof A Luft MD)**, University of Zurich, Zurich, Switzerland; Zürcher Höhenkliniken, Wald, Switzerland** (J Blanco MD, M Felder MD)**; Zentrum für Ambulante Rehabilitation, Zurich, Switzerland** (K Campen, Prof A Luft)**; Reha Rheinfelden, Rheinfelden, Switzerland** (Prof T Ettlin MD, C Schuster-Amft PhD)**; ARTORG Center for Biomedical Engineering Research, Gerontechnology and Rehabilitation, University of Bern, Bern, Switzerland** (Prof T Nef PhD)**; and Institute for Rehabilitation and Performance Technology, Bern University of Applied Sciences, Burgdorf, Switzerland** (C Schuster-Amft)

Correspondence to: Dr Verena Klamroth-Marganska, Sensory-Motor Systems Lab, Institute of Robotics and Intelligent Systems, Department of Health Sciences and Technology, ETH Zurich, Tannenstrasse 1, 8092 Zurich, Switzerland **verena.klamroth@hest.ethz.ch**

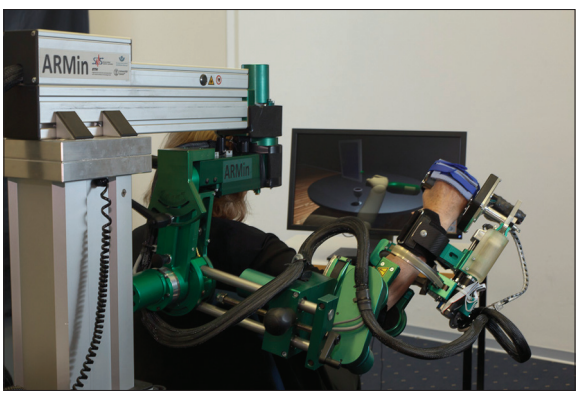

Figure 1: **Patient doing task-oriented training (filling a glass) with ARMin**

tunnel width, and gravitational and movement assistances are adjusted by the therapist (patient-cooperative path controller[11]).

We aimed to address whether robotic training of an affected arm with ARMin after stroke reduces motor impairment with respect to arm and hand function more effectively than does conventional therapy. Furthermore, we investigated whether robotic therapy with ARMin had long-term effects on impairment, activity, and participation (ie, social functioning),[1] and which subpopulations benefit most from the intervention.

Methods

Study design and participants

Our multicentre, parallel-group randomised trial was designed as a proof-of-concept study testing safety and preliminary efficacy (phase 2 or stage 3 according to Dobkin[18]). Four clinical centres in Switzerland (Uniklinik Balgrist, Reha Rheinfelden, Zentrum für Ambulante Rehabilitation Zürich, and Zürcher Höhenklinik Wald) were involved in recruitment and therapy. Zürcher Höhenklinik Wald and Reha Rheinfelden are neurorehabilitation centres in the metropolitan areas of Zurich and Basel, respectively, each with a catchment area of about 1·2 million people. Through inpatient and outpatient facilities, between 300 and 600 patients are treated at each centre after cerebrovascular accidents annually. Zentrum für Ambulante Rehabilitation Zürich is an outpatient clinic for neurorehabilitation situated in Zurich, and more than 100 patients are treated there after cerebrovascular accidents every year. Uniklinik Balgrist is the clinical partner for technical development of the ARMin robot and is situated in Zurich. Specialised therapy of patients with spinal cord injury is given at this clinic, with about 240 patients treated per year. Patients with spinal cord injuries and those with other neurological motor disorders are treated as outpatients in this clinic.

Patients were recruited through the centres and media (advertisements in newspapers and on television). They were eligible if they met inclusion criteria (panel 1), such as a diagnosis of one cerebrovascular accident, chronic motor impairment, and moderate-to-severe arm paresis. To confirm chronic impairment, patients were assessed again with the Fugl-Meyer assessment (FMA-UE) 3–4 weeks after the initial assessment; they were only included in the study when the difference between assessments was 3 points or less.

Because of difficulties with enrolment of the planned number of patients, after 19 months, the study and recruitment period were extended by 17 months and the eligibility criteria were widened. Originally, we had specified that individuals had to have had an ischaemic stroke, but we extended the criterion to cerebrovascular accident. Additionally, we discarded an exclusion criterion so that patients with epilepsy became eligible, and the age restriction changed from 18–80 years to at least 18 years. Patients who had not been originally considered or had been ineligible because of the original criteria were contacted and offered testing for eligibility. Because of recruitment difficulties at Zürcher Höhenklinik Wald, five allocation envelopes were transferred from there to Uniklinik Balgrist.

Data management and monitoring, and administration were controlled by the study co-ordinator (VK-M). The principal investigators of each of the clinical centres approved all decisions and met annually to ensure the study was proceeding according to protocol. The study procedures were approved by the respective institutional review boards of each participating centre. Participants provided written informed consent before enrolment.

Randomisation and masking

Patients were randomly assigned (1:1) to receive robotic or conventional therapy, using a centre-stratified randomisation procedure with one block of 20 patients for each centre. A computer-generated list of random numbers was used, which paired a unique sequential number with a treatment type (robotic or conventional). Pairs were sealed in tamper-evident envelopes by the study co-ordinator. Each centre received 20 envelopes. Assessors were masked to treatment allocation, but patients, therapists, and data analysts were unmasked. The clinical tests FMA-UE and the Wolf Motor Function Test were taped so that they could be reviewed at a later stage if necessary. Clinical centres and group assignment were coded during data processing to avoid bias in reporting, data processing, and data analysis. For each participant, all recorded data were crosschecked by a study nurse not involved in data collection.

For more on the **computer-generated list** see http://www.randomizer.org

Procedures

For both groups, therapy was given three times a week in the centres for a period of 8 weeks (total 24 sessions). Only one session per day could be scheduled. Up to four missed sessions could be rescheduled as long as training duration did not exceed 9 weeks. The minimum time for each session (excluding time for preparation, diagnostics, and documentation) was 45 min.