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Influence of single centers in a multicenter trial on robot-assisted therapy?*

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Abstract— **Stroke is one of the leading causes of disability, and advances in neurorehabilitation bring new therapy forms that aim to enhance recovery after stroke. In a multicenter clinical trial, we tested whether robot-assisted therapy of the arm with the therapy robot ARMin is superior to conventional therapy with regard to improvement in arm motor function. In this article, we describe differences in motor function gains among the four participating centers. Three centers showed a tendency favoring robotics whereas one center showed the converse. Results might be accidental considering the small and different number of patients within the centers. However, it indicates that not only study procedures but soft factors that are generally not taken into consideration when planning a multicenter study, such as therapeutic attitude or center differences, might influence the study outcome.**

I. Introduction

Stroke is among the most common causes of long term disability in adults [1] and multiple disciplines from research and clinics collaborate with the shared goal to enhance motor recovery after stroke. In order to test new concepts for effectiveness, multicenter trials (MCT) are a powerful option as they may allow more conclusions than monocentric studies. A MCT is a "clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator"[2]. We had conducted a MCT in order to test for superiority of robot-assisted therapy of the arm after stroke in comparison to conventional, physical and occupational therapy [3]. Robot-assisted therapy was applied with the therapy exoskeleton ARMin, a robot that allows for training of tasks of daily living and games in a virtual environment [4]. The device was developed by a team of engineers, therapists and physicians (ETH Zurich and the Spinal Cord Injury Center, University Hospital Balgrist) and successfully tested in four clinical centers on patients in the chronic state after stroke. Main outcome measure was the upper motor section of the Fugl-Meyer Assessment (FMA), a clinical tool to test motor function of the arm, particularly after stroke. In our previous analysis, we had added the center as a random effect to reduce the amount of unexplained variation, thus increasing the accuracy of the estimates. Although the clinical relevance may be questionable, we could show that the robotic therapy group gained significantly more points in motor function of the arm: the mean change was 3.25 points (SD 1.68) with robotic therapy and 2.47 points (SD 1.67) with conventional therapy. In the present study, we aimed to inspect the role of the four centers and the analysis for FMA was split by center in order to study group effects within the centers.

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II. Methods

Details on this prospective, multicenter, controlled, parallel-group, single-blind (examiner-blind) demonstration-of-concept trial were described before [3]. The study was registered with ClinicalTrials.gov, number NCT00719433.

A. Participating centers

Four clinical centers in the German-speaking part of Switzerland participated in the trial (Zürcher Höhenklinik Wald ZHW, Uniklinik Balgrist UKB, Reha Rheinfelden RRh, and Zentrum für Ambulante Rehabilitation Zürich ZAR). ZHW and RRh are major neurorehabilitation centers in the agglomeration of Zurich and Basel with inpatient and outpatient facilities and a catchment area of approximately 1.2 million individuals each. Each center treats between 400 and 600 patients after cerebrovascular accidents (CVA) annually. ZAR is a specialized outpatient clinic for neurorehabilitation situated in the city of Zurich with more than 100 patients after CVA treated every year. UKB is the clinical partner for technical development of the ARMin robot and situated in the city of Zurich. Main focus is on spinal cord injuries, but patients with other neurological motor disorders are treated as outpatients in this clinic. All the participating centers are experienced in clinical research projects. In UKB and ZHW, an occupational therapist, and in RRh, a physical therapist conducted all the therapies (with a trained substitute). In ZAR, both a physical therapist and an occupational therapist were involved regularly in the study but each patient was treated only by one person (also with trained substitutes).

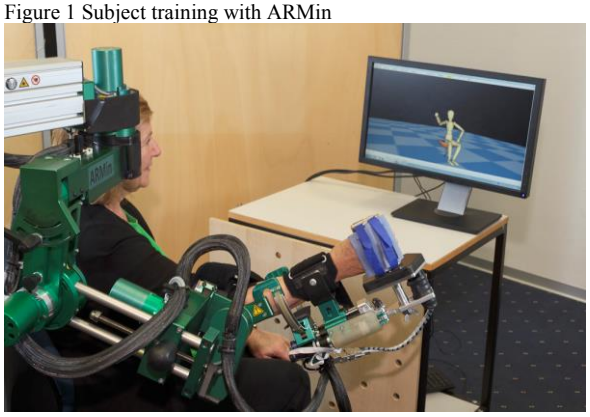
B. Patients and Therapies

The planned sample size was 80 participants. Patients were randomly assigned (1:1) to receive either robotic or conventional therapy, using a center-stratified randomization procedure with one block of 20 patients for each center. Patients in both groups received 24 sessions of therapy, administered evenly throughout eight weeks (i.e. three times per week). Conventional and robotic trainings were performed by the same therapists that had more than four years of professional experience. Patients were assigned to therapists before randomization. Prior to the study each therapist received several hours of teaching in robotic therapy

by an instructed therapist and an engineer responsible for the ARMin device at each center. This training involved one-to-one-training, observation at therapies and supervised training with patients. All therapists met at least once a year to assure compliance with the protocol and to report about study progress.

The ARMin device (Figure 1) comprises three modes of therapy: During patient-passive mobilization, the therapist moves the patient's arm on an arbitrary but patient-individual trajectory, while the robot actively compensates friction and gravity. The recorded movement can be repeated by the robot while the patient is instructed to remain inactive. Active-assisted games (e.g., a ball game) can be adjusted in difficulty and complexity as performance of arm movements improves. Special focus was put on the design of active-assisted training of activities of daily living (ADL) in an enriched environment (e.g. filling a glass, cutting bread, cleaning a table) that engage the patient actively and are intuitive to understand.

Figure 1 Subject training with ARMin



Patients in the robotic group performed these three modes of therapy in each session for a minimum of ten minutes each under supervision of a therapist.

The control group received conventional physical or occupational therapy, usually including mobilization, games, and training of ADL. Individual treatment was delivered in the therapy facilities of the corresponding clinic by a therapist. Mobilization, games, and ADL training had to be performed, but no further guidelines for the form of therapy or methods used were given in order to achieve an active control group that represents the common clinical rehabilitation practice for chronic stroke patients. Only restriction was not to use technical devices.

Each training session in both, the ARMin group and in the control group, consisted of 45 to 60 minutes of mere therapy, up to 15 minutes were allowed for preparations.

A. Assessments

The five clinical examiners who performed the tests had an educational background in occupational or physical therapy or as a physician-in-training. They were responsible for the testing procedures and underwent a standardization lead by an instructed therapist at the ETH Zurich which included a theoretical and practical education program and supervised practice on patients before initiation of the study. They met at least once a year to assure compliance with the protocol. Patients were assessed with a battery of clinical tests, questionnaires, and measurement with the ARMin robot, immediately before therapy, after 4 weeks of therapy (t1, half of therapy), after eight weeks (t2, end of therapy), 16 weeks (t3, follow-up) and 34 weeks after start of therapy (t4, follow-up). Results were published [3].

The FMA is a test of 33 tasks that assesses motor function of the arm after stroke. The score ranges from 0 points (no function, no reflexes) to a maximum of 66 points (no deficit). Validity, reliability, and responsiveness of the FMA are established [5-7].

Training, administration, data management and data monitoring were arranged and supervised by ETH Zurich. The principal investigators of each of the clinical sites made and approved all decisions concerning the conduct of the study and met annually to assure conductance according to the protocol. Study procedures were approved by the respective institutional review boards of each participating site (Cantonal Ethical Committees).

B. Data Analysis

All calculations were done with SPSS (version 20.0), a *p*-value of <0.05 was chosen as significant. The calculation of the sample size was based on the data of the FMA of a comparable robot-aided arm therapy study [8]. The distribution patterns of baseline characteristics (sex, age in years at therapy, time since stroke in months, dominant arm affected, severity of motor impairment at baseline as measured by FMA, mean strength at baseline as measured by ARMin, location of stroke (cortical vs. subcortical) or stroke size ($>$ or $\leq$ 2 cm)) between the four centers were compared with ANOVA. We used a repeated measures linear mixed model to assess the effect of treatment over the entire course of the study for each of the outcome measures. Data were split by centers; group was used as between-subject factor, FMA at baseline and time since stroke (in months) as covariates.

III. RESULTS

Seventy-three subjects were eligible and were analyzed for the study. Thirty-eight patients were assigned to robotic therapy and 35 were assigned to conventional therapy. Because of recruitment difficulties at ZHW, five allocation envelopes were transferred from there to UKB. At UKB, 25 patients (13 with robotic therapy, 12 with conventional therapy), at ZAR, 19 patients (11, eight), at ZHW, 11 patients (five, six), and at RRh, 18 patients (nine, nine) were included into analysis. We do not report names of centers in the results to avoid potential reputational consequences.

No significant differences in subject baseline characteristics between the hospitals could be observed (data not shown). In the linear mixed model analysis, two centers showed significant differences between the two therapy groups (robotic vs. conventional therapy) over the course of the study (Table 1).

TABLE 1 PRIMARY OUTCOME FMA WHEN SPLITTING BY CENTERS

Center	F ratio	P value	95% Confidence Intervals
A	1.98	0.16	-0.39 to 2.28
B	4.75	0.03	0.15 to 3.48
C	16.2	0.00	1.51 to 4.75
D	2.05	0.16	-1.96 to 0.32

At the end of therapy (after eight weeks), one center showed significant differences between the ARMin and the control group (Table 2 and Figure 2).

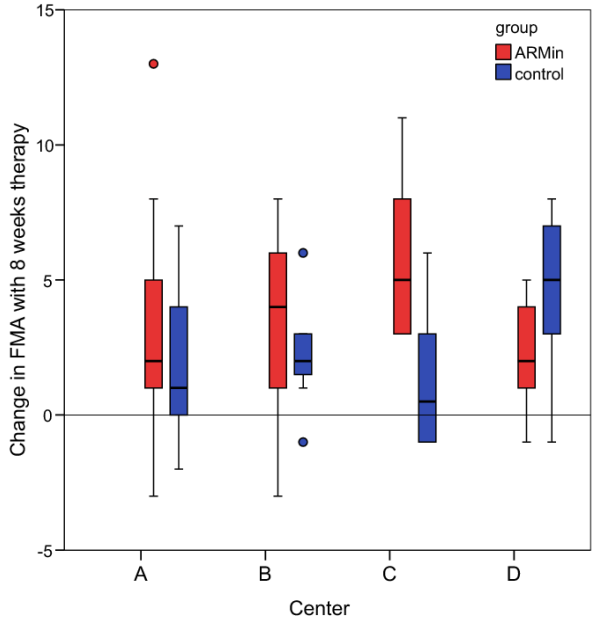
TABLE 2 DIFFERENCES IN FMA BETWEEN ROBOTIC AND CONTROL GROUPS AFTER EIGHT WEEKS OF THERAPY WHEN SPLITTING BY CENTERS

Center	mean difference (ARMin to control)	p value	95% Confidence Intervals
A	1.94	0.187	-1.01 to 4.89
B	2.19	0.179	-1.13 to 5.51
C	4.98	0.047	0.08 to 9.88
D	-2.34	0.072	-4.91 to 0.24

IV. DISCUSSION

A MCT allowed us to recruit sufficient subjects within a reasonable time-frame. These advantages were offset by demands on a well-functioning infrastructure. We abided on the suggestions of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH"). This means we intended that the way "the protocol is implemented should be clear and similar at all centers", and that "procedures were standardized as completely as possible". Furthermore, "variation of evaluation criteria and schemes were to be reduced by investigator meetings, by the training of personnel in advance of the trial and by careful monitoring during the trial"[2]. Still, we could not prevent different outcomes among the participating centers, although these might be well accidental.

Figure 2 Change in FMA within centers after eight weeks therapy



In two centers, significant differences in FMA between the therapy groups could be observed over the whole course of the study. In the other two centers, no significant differences between the therapy groups could be seen. When limiting the analysis on the change after eight weeks of therapy (without follow-up), significance could be found in only one center (Figure 2).

This is not surprising considering the small sample sizes when each center is analyzed separately.

Nevertheless, there was a general tendency in favor of one therapy form or the other at the centers. Three centers showed a tendency towards an added value favoring robotics whereas one center showed the converse. It is likely that these results are due to chance alone, as both number of patients and proportions of treated patients varied by center and patient numbers in the single centers were small.

But results might suggest that the study outcome was influenced by additional factors that are generally not taken into consideration when planning a multicenter study. Such (e.g. transport facilities, indoor climate) or differences in therapeutic quality (e.g. professional experience, therapy focus, and attitude toward different therapy forms). We did not investigate the influence of these factors but would consider them as soft factors that can have an impact on the outcome of a MCT.

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