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Virtual Reality Training for Upper Extremity in Subacute Stroke (VIRTUES)

A multicenter RCT

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ABSTRACT

Objective: To compare the effectiveness of upper extremity virtual reality rehabilitation training (VR) to time-matched conventional training (CT) in the subacute phase after stroke.

Methods: In this randomized, controlled, single-blind phase III multicenter trial, 120 participants with upper extremity motor impairment within 12 weeks after stroke were consecutively included at 5 rehabilitation institutions. Participants were randomized to either VR or CT as an adjunct to standard rehabilitation and stratified according to mild to moderate or severe hand paresis, defined as ≥20 degrees wrist and 10 degrees finger extension or less, respectively. The training comprised a minimum of sixteen 60-minute sessions over 4 weeks. The primary outcome measure was the Action Research Arm Test (ARAT); secondary outcome measures were the Box and Blocks Test and Functional Independence Measure. Patients were assessed at baseline, after intervention, and at the 3-month follow-up.

Results: Mean time from stroke onset for the VR group was 35 (SD 21) days and for the CT group was 34 (SD 19) days. There were no between-group differences for any of the outcome measures. Improvement of upper extremity motor function assessed with ARAT was similar at the postintervention ($p = 0.714$) and follow-up ($p = 0.777$) assessments. Patients in VR improved 12 (SD 11) points from baseline to the postintervention assessment and 17 (SD 13) points from baseline to follow-up, while patients in CT improved 13 (SD 10) and 17 (SD 13) points, respectively. Improvement was also similar for our subgroup analysis with mild to moderate and severe upper extremity paresis.

Conclusions: Additional upper extremity VR training was not superior but equally as effective as additional CT in the subacute phase after stroke. VR may constitute a motivating training alternative as a supplement to standard rehabilitation.

ClinicalTrials.gov identifier: NCT02079103.

Classification of evidence: This study provides Class I evidence that for patients with upper extremity motor impairment after stroke, compared to conventional training, VR training did not lead to significant differences in upper extremity function improvement. ***Neurology*® 2017;89:1–9**

GLOSSARY

ARAT = Action Research Arm Test; **BBT** = Box and Blocks Test; **FIM** = Functional Independence Measure; **PGIC** = Patient Global Impression of Change; **UE** = upper extremity; **VIRTUES** = Virtual Reality Training for Upper Extremity in Subacute Stroke; **VR** = virtual reality.

Virtual reality (VR) systems are regarded as promising new tools for rehabilitation. Results from research suggest that VR comprises motivating tasks that facilitate many repetitions at a high intensity and promote a diversity of movements while providing salient stimuli.[1–3] One of the most relevant areas of application is upper extremity (UE) motor training after stroke because a large patient group is affected.[4] A growing number of studies, mostly with patients in the chronic phase after stroke, indicate that the use of VR for UE rehabilitation may be

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beneficial.[5,6] Few studies enrolled patients in the acute and subacute phases. While small-scale studies also indicated a favorable effect of VR on UE motor function,[7,8] the only larger studies to date found no superiority of VR training.[9,10] However, in these studies, commercial gaming systems, not necessarily suitable for rehabilitation purposes, were applied. Commercial gaming consoles are developed for healthy persons and offer very limited possibilities of adjustment.[11] The provided gaming options can be too challenging for elderly and severely to moderately impaired patients.[3] VR systems for rehabilitation purposes, on the other hand, allow stepwise adaption to increasing motor abilities.[12] Principles of motor control and plasticity such as intensity, repetitions, increasing difficulty, and motivation provide to a varying degree the conceptual basis of many systems.[13,14] VR technology has the potential to increase the intensity of training and to add exercise options, especially for patients with severe distal paresis.[15] Thus, VR systems designed for rehabilitation purposes may maximize the increased rehabilitation potential early after stroke also for patients with severe deficits in the wrist and hand.[16]

There are to date no adequately powered trials looking at the efficacy of VR rehabilitation systems in the subacute phase after stroke including patients with severe impairments. The Virtual Reality Training for Upper Extremity in Subacute Stroke (VIRTUES) trial is a large multicenter phase III randomized controlled trial in which patients in the subacute phase were enrolled and stratified according to severity of wrist and hand paresis. The objective of this study was to compare VR training to time-matched conventional training (CT), both provided as an adjunct to standard rehabilitation. We hypothesized that VR training designed for rehabilitation purposes would be more effective in improving UE motor function than CT for patients with mild to moderate and severe distal paresis.

METHODS

Primary research questions/classification of evidence. Our primary research question was to examine whether additional VR training was superior to additional CT. This study provides Class I evidence that VR training did not lead to significant differences in UE function improvement.

Study design and participants. VIRTUES was a randomized, single-blinded, international multicenter trial conducted at 5 rehabilitation hospitals in Europe. A total of 120 patients were included. All patients with a diagnosis of stroke (cerebral infarction or hemorrhage) admitted to the participating rehabilitation centers were screened for inclusion by the local research staff.

The University of Bergen, Norway, coordinated this trial in collaboration with Haukeland University Hospital and Sunnaas Rehabilitation Hospital in Norway, Hammel Neurocenter and Skive Neurorehabilitation in Denmark, and Jessa Hospitals and KU Leuven in Belgium. Statistical analyses were carried out at the Competence Center for Clinical Research, Haukeland University Hospital, Bergen, Norway. We performed double data entry to reduce transcription errors.[17] Patients >18 years of age who were able and willing to give informed consent were included if they had an ischemic or hemorrhagic stroke confirmed by CT or MRI and were within 3 months of stroke. Only patients with first-ever stroke or former stroke without any lasting motor impairment were included. Motor criteria included impaired arm motor function but some residual arm motor activity as defined by a score of <52 on the Action Research Arm Test (ARAT) as an upper limit and ability to execute at least 20° of active shoulder flexion and abduction against gravity as a lower limit. Patients were excluded if they had severe cognitive deficits defined as <20 on the Mini-Mental State Examination. Other exclusion criteria included conditions limiting the ability to comply with the treatment regimen such as orthopedic impairment limiting mobility substantially or causing pain in the affected arm or visual disorders.

Randomization and masking. The Unit of Applied Clinical Research, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway, administered the randomization through a centralized web-based randomization system. The system assigned patients randomly to either VR training or CT as an adjunct to standard rehabilitation. The patients were stratified according to the severity of wrist and hand paresis within each center, and blocks of 4 were used. We defined mild to moderate distal paresis as the ability to extend the wrist at least 20° and the fingers at least 10° from drop hand position and severe distal paresis as not being able to do so. Trained research staff, external or from other wards, masked for the allocation of the patients conducted all assessments.

Procedures. The participants received the additional interventions for up to 30 days after inclusion with a target of 4 to 5 training sessions per week of up to 60 minutes' duration. Designated research therapists provided both the VR training and the CT as an addition to standard rehabilitation. The amount of physical and occupational therapy provided was registered for each patient.

Patients randomized to the experimental group participated in VR training with the YouGrabber system (YouRehab Ltd, Schlieren, Switzerland). It consists of data gloves with sensors, an infrared camera, and software in combination with a personal computer and a screen. Developed for rehabilitation purposes, it comprises several games that the therapist can adapt to the patient's actual motor abilities. The different therapy modes include reaching and grasping exercises, selective finger movements, supination/pronation, whole-arm movements, unimanual or bimanual training, and virtually enhanced movements, i.e., movements that can be visually increased on the screen. Game parameters that could be adjusted were, among others, speed of objects, intervals between objects, and dispersion to the left and right of object positions.

Patients randomized to the control group participated in CT under supervision of a therapist to match the therapy time provided in the experimental group. Conventional arm training was based on a set of standardized exercises with an emphasis on task-related practice. It included exercises for different gross movements and dexterity using a variety of grips and selective finger movements. Further details are described elsewhere.[18]

Outcomes. We developed a comprehensive assessment manual to ensure standardized performance of all assessments. The patients were assessed at baseline (<72 hours before intervention start), after treatment (within 72 hours), and at the 3-month (±1 week) follow-up.

The primary outcome measure was UE motor function assessed with the ARAT after intervention. The ARAT covers a broad array of arm and hand activities, is widely used, and has excellent psychometric properties.[19] Secondary outcome measures included the Box and Blocks Test (BBT) as an assessment of dexterity[20] and the Functional Independence Measure (FIM) to reflect independence in activities of daily living.[21] Participants were asked to rate their difficulty of performing bimanual tasks with the ABILHAND after treatment and at the 3-month follow-up. ABILHAND is a Rasch-based questionnaire with higher scores indicating better bimanual performance.[22] Patients' general impression of improvement reflected by the Patient Global Impression of Change (PGIC) scale was likewise assessed after treatment and at the 3-month follow-up. PGIC is a 7-point scale ranging from very much worse (7) to very much better (1).

Standard protocol approvals, registrations, and patient consents. The Norwegian Regional Committees for Medical and Health Research (protocol 2013/0663) and the local ethics committees approved the trial. Written informed consent for participation was obtained from all patients. This trial has been registered at ClinicalTrials.gov (NCT02079103).

Statistical analysis. The power calculation was based on a clinically meaningful change of 6 points on ARAT, with a statistical power of 80% and $\alpha = 5\%$.[19] An SD of 11 points was estimated. A required sample size of 106 patients for 2 groups was calculated, 53 in each group. The recruitment of 120 patients was intended to compensate for a 10% dropout at the 3-month follow-up assessment.

To examine the association between treatment and improvement of UE motor function and independence in daily activities, we used linear regression models and graphical methods. We fitted for selected outcomes (ARAT, BBT, FIM, FIM motor scale) the linear mixed-effects model with treatment, time, and their interaction as independent variables with simple contrasts in time domain. This was done both unadjusted and adjusted for distal paresis and center. In addition, we estimated the same linear mixed-effects model stratified for distal paresis both unadjusted and adjusted for center. The patient-reported ABILHAND and PGIC data were analyzed with *t* tests. SPSS 22 (IBM Corp, Armonk, NY), R 3.3[18] with the nlme 3.1 package (R Foundation for Statistical Computing, Vienna, Austria),[19] and Matlab 7.10 (MathWorks Inc, Natick, MA) were used for data analysis. The significance level was set to 0.05.

RESULTS Between March 1, 2014, and April 12, 2016, a total of 1,224 patients were screened at admission to the rehabilitation centers. Of those, 1,079 did not meet the inclusion criteria, and 25 declined to participate (figure 1). The main reasons

Figure 1 Flowchart of patients through the trial

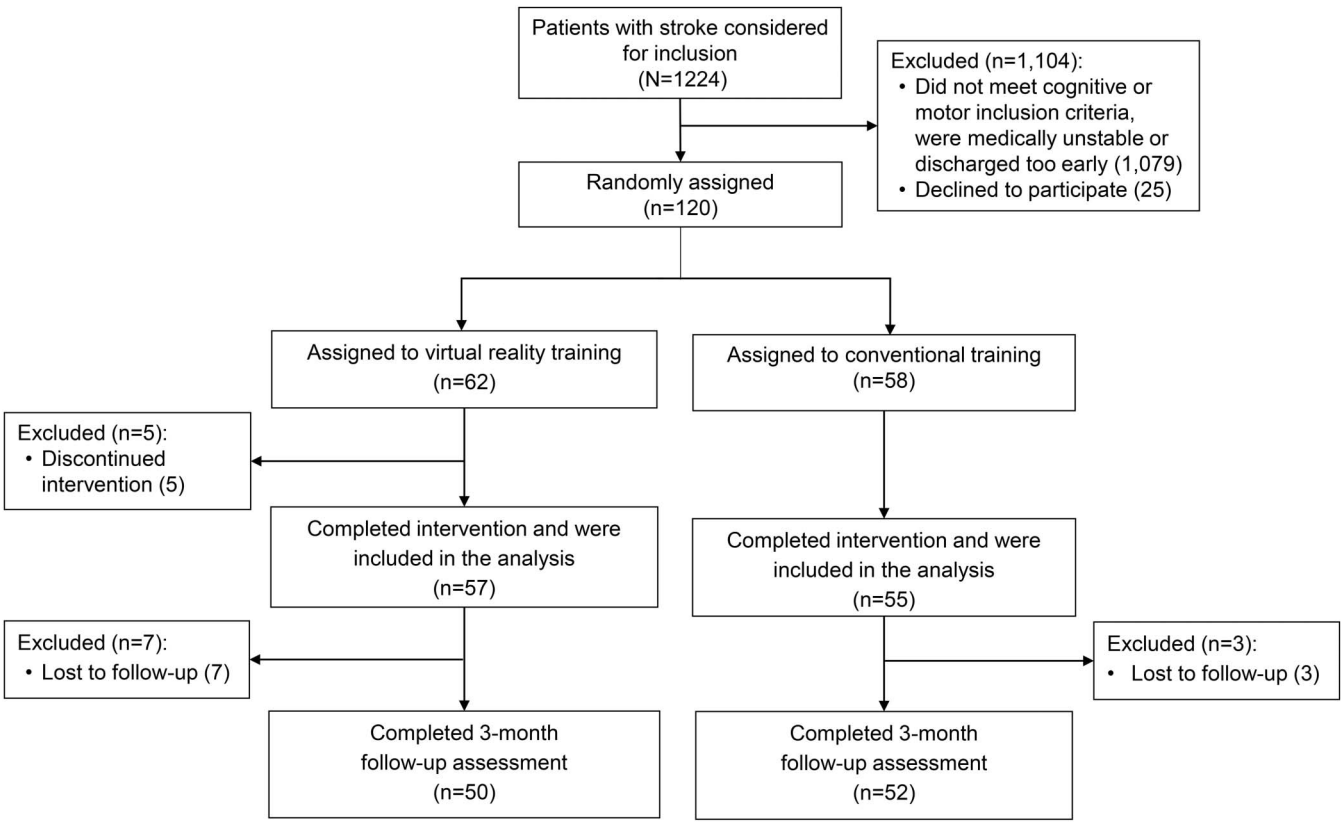


Table 1 Baseline and demographic characteristics

	VR training (n = 62)	CT (n = 58)
Age, mean (minimum–maximum), y	62 (23–89)	62 (41–87)
Sex, n (%)		
Male	42 (68)	35 (60)
Female	20 (32)	23 (40)
Handedness, n (%)		
Left	8 (13)	4 (7)
Right	54 (87)	54 (93)
Affected arm, n (%)		
Left	40 (65.5)	27 (47)
Right	22 (35.5)	31 (53)
Severity of paresis at inclusion, n (%)		
Mild to moderate	37 (60)	31 (53)
Severe	25 (40)	27 (47)
Stroke type, n (%)		
Infarction	47 (76)	48 (83)
Hemorrhage	15 (24)	10 (17)
Stroke location, n (%)		
Cortical	21 (34)	19 (33)
Subcortical	30 (48)	24 (41)
Cerebellum/brainstem	8 (13)	12 (21)
Unknown	3 (5)	3 (5)
Comorbidities, n (%)		
Hypertension	14 (23)	15 (26)
Myocardial infarction	6 (10)	10 (17)
Atrial fibrillation	1 (2)	2 (3)
Diabetes mellitus	3 (5)	6 (10)
Peripheral artery disease	1 (2)	3 (5)
Dyslipidemia, obesity and other	30 (48)	22 (38)
Mini-Mental State Examination score	27.8 (2)	28 (2.3)
Apraxia Screening Test score (maximum 12 = best)	11.7 (1.2)	11.7 (1.2)
Star Cancellation Test score	0.45 (0.15)	0.42 (0.18)
Days after stroke at randomization	35 (21)	34 (19)
Sessions, n	17 (3)	16 (3)
Duration of intervention, min	816 (210)	892 (248)
Duration of other PT/OT during the intervention, min	1,759 (791)	1,780 (879)

Abbreviations: CT = conventional training; OT = occupational therapy; PT = physical therapy; VR = virtual reality.

for not being eligible were no UE impairment, too good or too poor UE motor function, and cognitive impairment. Of the 120 eligible patients, 62 were randomly assigned to additional VR training (intervention; VR) and 58 to additional CT (active control group; CT). Eight patients discontinued the intervention because of medical or personal reasons unrelated to the study, 5 in VR and 3 in CT. No adverse events were reported. The remaining 112 patients were included in the postintervention analysis. Ten patients were not available for the 3-month follow-up, 7 in VR and 3 in CT, leaving 102 patients who participated.

There were no statistical differences with regard to baseline characteristics, duration of training, and standard rehabilitation provided between the patients in VR and CT (table 1).

The results of the linear mixed model estimation are shown in table 2, showing the measured mean values at the different time points, and illustrated in figure 2. We found a significant improvement of all outcomes independently of treatment ($p < 0.001$). However, there was no significant difference according to type of treatment (VR or CT) in both the unadjusted and adjusted or stratified models for any of our outcomes after intervention and at follow-up (table 2 and figure 2). For ARAT, patients in VR improved a mean of 12 (SD 11) points (21%) from baseline to the postintervention assessment and 17 (SD 13) points (30%) from baseline to follow-up, whereas patients in CT improved 13 (10) points (21%) between baseline and the postintervention assessment and 17 (13) points (30%) between baseline and follow-up.

Results for the subgroups of distally severe and mild to moderately impaired patients were also nonsignificant for any of the outcome measures after intervention and at follow-up (table 2 and figure 2). On ARAT, patients with mild to moderate wrist and hand paresis improved 14 (9) points (25%) in VR and 13 (9) points (23%) in CT from baseline to follow-up. Patients with severe distal paresis improved 23 (17) points (40%) in VR and 23 (16) points (40%) in CT at follow-up. A follow-up score of 30 (20) in VR and 31 (18) in CT implies still limited UE motor function for many of the patients. This is also reflected by the BBT: patients with severe distal paresis in VR were able to move 19 (15) blocks and patients in CT could move 18 (15) blocks in 1 minute, as opposed to mild to moderately impaired patients who moved 43 (15) blocks in VR and 39 (16) in CT.

Patient-reported data on improved UE motor function were collected after intervention and at follow-up. The ability to perform bimanual tasks as reflected by the ABILHAND questionnaire was similar for both groups at the postintervention and 3-month follow-up assessments (table 2). Comparably, patients in VR and CT rated their impression of improved UE motor function >2 on PGIC, which means much better (1 = very much better) (table 2).

DISCUSSION We report a large multicenter trial using specifically designed VR rehabilitation technology for patients in the subacute phase after stroke having mild to moderate and severe wrist and hand

Table 2 Baseline, postintervention, and 3-month follow-up for ARAT, BBT, FIM, and FIM motor scale and postintervention and 3-month follow-up for ABILHAND and PGIC

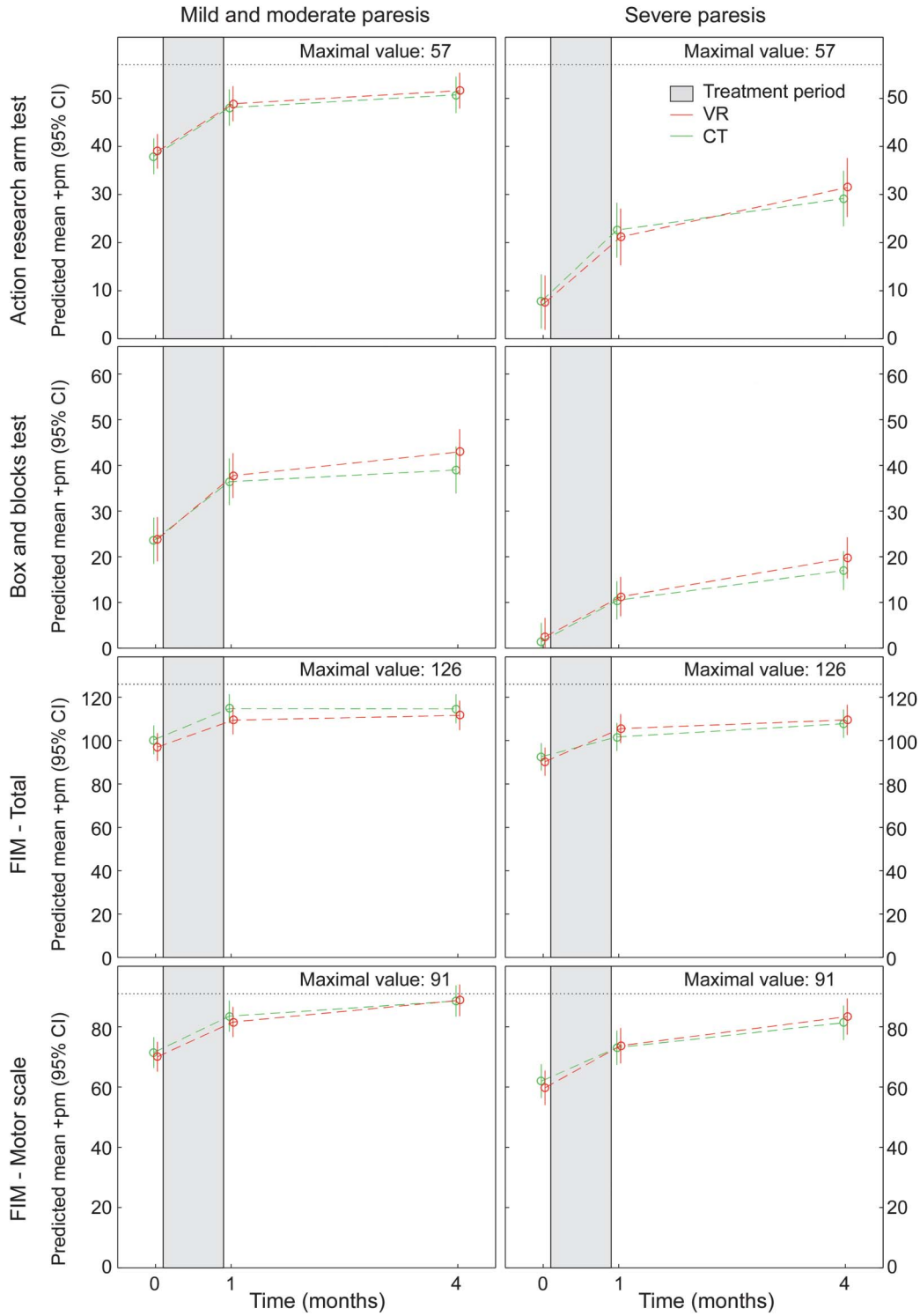
	All patients (n = 120)				Severe paresis (n = 52)				Mild to moderate paresis (n = 68)			
			Change				Change				Change	
	VR, mean (SD)	CT, mean (SD)	B (95% CI)	*p* Value	VR, mean (SD)	CT, mean (SD)	B (95% CI)	*p* Value	VR, mean (SD)	CT, mean (SD)	B (95% CI)	*p* Value
ARAT												
Baseline	25.8 (18.3)	24.2 (18.6)	—	—	7.3 (5.9)	8.4 (8.7)	—	—	38.1 (12.3)	38.2 (12.8)	—	—
After intervention	37.7 (19.5)	36.8 (18.8)	−0.8 (−4.8 to 3.2)	0.705	20.4 (17.3)	24.2 (15.2)	−1.0 (−8.5 to 6.4)	0.789	49.2 (10.1)	48.2 (14.0)	−0.2 (−3.7 to 3.3)	0.905
Follow-up	43.0 (17.7)	41.5 (18.0)	0.6 (−3.5 to 4.8)	0.770	30.1 (19.5)	30.9 (18.2)	2.6 (−5.1 to 10.3)	0.522	51.6 (9.4)	50.9 (11.8)	−0.1 (−3.7 to 3.6)	0.977
BBT												
Baseline	14.2 (14.2)	13.5 (14.9)	—	—	2.2 (4.0)	2.0 (4.7)	—	—	23.8 (12.3)	23.4 (13.96)	—	—
After intervention	26.0 (18.7)	25.0 (19.1)	0.6 (−3.0 to 4.2)	0.740	11.1 (12.1)	11.5 (10.9)	−0.1 (−5.8 to 5.6)	0.969	38.0 (13.7)	36.7 (17.4)	1.1 (−3.4 to 5.5)	0.636
Follow-up	33.2 (18.7)	29.3 (18.7)	2.7 (−1.0 to 6.5)	0.154	19.3 (14.9)	18.2 (14.98)	1.9 (−4.0 to 7.7)	0.548	42.5 (15.0)	39.1 (16.2)	3.8 (−0.8 to 8.4)	0.115
FIM												
Baseline	94.3 (19.6)	96.3 (19.5)	—	—	91.9 (17.1)	94.5 (15.1)	—	—	96.8 (18.4)	102.5 (19.2)	—	—
After intervention	107.7 (14.6)	108.7 (14.3)	1.9 (−4.5 to 8.3)	0.563	105.8 (12.7)	102.1 (16.1)	6.2 (−2.8 to 15.3)	0.191	110.0 (15.0)	114.9 (8.3)	−1.7 (−10.6 to 7.3)	0.725
Follow-up	111.2 (20.6)	112.7 (16.0)	1.9 (−4.7 to 8.5)	0.570	109.6 (21.2)	107.9 (18.3)	4.4 (−5.0 to 13.7)	0.373	112.3 (20.9)	116.6 (12.7)	0.2 (−9.1 to 9.4)	0.975
FIM motor												
Baseline	65.7 (15.9)	66.9 (17.5)	—	—	60.6 (15.1)	63.3 (14.8)	—	—	70.4 (13.1)	73.5 (16.4)		
After intervention	78.1 (12.7)	79.0 (13.1)	1.0 (−3.7 to 5.7)	0.672	73.7 (11.1)	74.1 (16.3)	2.8 (−3.3 to 9.0)	0.377	82.1 (12.2)	84.0 (6.6)	−0.5 (−7.4 to 6.5)	0.899
Follow-up	86.9 (12.6)	85.5 (15.1)	2.8 (−2.1 to 7.6)	0.269	83.6 (12.3)	81.9 (18.8)	4.4 (−2.0 to 10.7)	0.188	89.1 (12.4)	88.5 (10.3)	1.6 (−5.5 to 8.7)	0.664
	Mean (SD)	**Mean (SD)**	**Mean difference**	***p* Value**	**Mean (SD)**	**Mean (SD)**	**Mean difference**	***p* Value**	**Mean (SD)**	**Mean (SD)**	**Mean difference**	***p* Value**
ABILHAND												
After intervention	1.56 (2.13)	1.53 (1.97)	0.03	0.246	0.41 (1.48)	0.5 (1.0)	0.09	0.80	2.3 (2.2)	2.4 (2.2)	0.1	0.870
Follow-up	2.56 (1.97)	2.4 (2.04)	0.16	0.668	1.65 (0.37)	1.45 (0.30)	0.20	0.53	3.2 (2.0)	3.3 (2.0)	0.1	0.820
PGIC												
After intervention	1.98 (0.74)	1.82 (0.74)	0.16	0.923	2.18 (0.67)	2.04 (0.74)	0.14	0.494	1.86 (0.77)	1.63 (0.72)	0.23	0.234
Follow-up	1.82 (0.77)	1.81 (1.07)	0.01	0.947	2.05 (0.89)	2.0 (1.41)	0.05	0.892	1.67 (0.121)	1.64 (0.621)	0.03	0.888

Abbreviations: ARAT = Action Research Arm Test; BBT = Box and Blocks Test; CI = confidence interval; CT = conventional training; FIM = Functional Independence Measure; PGIC = Patient Global Impression of Change; VR = virtual reality.
Results are presented by treatment group, for all patients, and for the subgroups of patients with severe paresis and mild to moderate paresis.

paresis. Our hypothesis that additional VR is superior to additional CT for both subgroups of severity was not confirmed.

There are several possible explanations for this finding. It is likely that a potential difference in UE motor function was not large enough and undetectable in the context of spontaneous biological recovery.[23] As recently described, it is a challenge to reveal any significant differences in the acute/subacute phase if the contrast between the therapy dose in the intervention and control treatment is not large enough on the background of spontaneous biological recovery and

Figure 2 **Predicted means for patients with mild to moderate and severe paresis**



CT = conventional training; FIM = Function Independence Measure; VR = virtual reality.

other ongoing rehabilitation.[24] This is especially the case when the control treatment is time matched, as in our study. Even 3-armed studies including intervention, dose-matched control, and a third standard care condition were frequently not able to report differences, e.g., studies investigating task-oriented UE training[25] and circuit class training.[26]

The means of delivery, VR on the one hand and conventional exercises on the other, seem to be quite dissimilar. However, the contrast may have been too small with regard to the content of the training because both groups trained functionally.[4] Nevertheless, our study adds to the body of knowledge in the stroke rehabilitation domain for which initial evidence for a therapeutic approach was available from small-scale studies but a phase III trial could not confirm superiority.

Furthermore, it may be important to apply outcome measures that are able to differentiate between recovery on an impairment level and compensation.[27] Our main outcome measure, ARAT, although comprising elements that consider quality of movement, assesses UE motor function on an activity level. A battery of assessment tools including the impairment level such as kinematics may help to differentiate between different mechanisms of recovery.[28] There are indications that intensity of training during the first months after stroke is crucial for maximally exploiting the window of increased plasticity.[16] We found considerably increased active training time for severely impaired patients in the VR training group compared to the CT group.[15] However, this could not be translated into a larger improvement of arm motor function in the VR group. Results from animal studies suggest that high doses and many repetitions are required to induce behavioral changes after brain injury.[29] Even in studies in which high-intensity training in terms of many repetitions was examined, the dose rarely approached the recommendations derived from animal studies.[30] Hence, it is possible that the observed increased activity was still below a beneficial threshold for arm motor function. A recent systematic review suggested an increase of at least 240% in therapy time relative to standard rehabilitation.[31]

It seems particularly relevant to discuss our results in relation to a recently published study applying a commercial gaming device because this study is one of the few large-scale VR trials in which patients in the subacute phase were included.[10] Although the results in both studies were neutral, there are several differences. In the earlier study, only patients with mild to moderate motor impairment were included. VIRTUES also recruited a considerable number, $\approx$40%, of patients with severe impairment in the wrist and hand. Consequently, our results widen the applicability of VR to patients with a broad range of distal motor impairments. In VIRTUES, patients trained with a system developed for rehabilitation. VR training with a commercial system would not have been possible for the severely impaired patients in our study, and this is an important clinical message. These differences notwithstanding, the fact remains that both trials could not find superiority of VR-based therapy.

There are some limitations to consider. A design including a third arm receiving only standard rehabilitation would at least have given an impression if we added anything at all through more intensive training and increased training time, as previously suggested.[32] However, this was not the objective of our trial. VR training and CT training in our trial were provided as an add-on and made up only a part of the total rehabilitation for UE motor function provided. It is possible that the additional effect was not large enough to make a difference.

The applied VR system was not immersive in the sense of providing a real experience of being in another reality. We can only speculate whether a more immersive experience would have made a difference. New developments, e.g., the application of VR goggles, may possibly add another dimension and may increase the effect of motor training. Furthermore, remote VR telerehabilitation strategies for patients at home, which could lessen travel burden and costs, deserve further examination.

The addition of UE VR training was not superior to CT in the subacute phase after stroke for patients with mild to moderate and severe wrist and hand impairment. VR may constitute a motivating training alternative as a supplement to standard rehabilitation. In most patients, even those with initially severe distal paresis, arm motor function increased substantially. This implies that different training modalities can contribute to improvement and may be applied according to patient preference.

AUTHOR CONTRIBUTIONS

Iris Brunner and Jan Sture Skouen: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision, obtaining funding. Håkon Hofstad: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. Jörg Aßmus: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Frank Becker: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Anne-Marthe Sanders: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval. acquisition of data, study supervision. Hanne Pallesen: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, study supervision. Lola Qvist Kristensen: drafting/revising the manuscript, analysis or interpretation of data,

accepts responsibility for conduct of research and will give final approval, data collection. Marc Michielsen: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, study supervision. Liselot Thijs: study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis. Geert Verheyden: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision, obtaining funding.

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DISCLOSURE

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