Using a bimanual lever-driven wheelchair for arm movement practice early after stroke: a pilot, randomized, controlled, single-blind trial

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Complete List of Authors:	Smith, Brendan; Loyola Marymount University, Mechanical Engineering Lobo-Prat, Joan; University of California Irvine, Mechanical and Aerospace Engineering; Universitat Politecnica de Catalunya, Institut de Robòtica i Informàtica Industrial Zondervan, Daniel; Flint Rehabilitation Devices, LLC, N/A Lew, Christopher; University of California Irvine, Mechanical and Aerospace Engineering Chan, Vicky; University of California Irvine Medical Center, Rehabilitation Services Chou, Cathy; University of California Irvine Medical Center, Rehabilitation Services Toledo, Spencer; Rancho Los Amigos National Rehabilitation Center, Rehabilitation Services Reinkensmeyer, David; University of California Irvine, Departments of Anatomy and Neurobiology, Mechanical and Aerospace Engineering, Biomedical Engineering, and Physical Medicine and Rehabilitation Shaw, Susan; Rancho Los Amigos National Rehabilitation Center, Neurology; Epilepsy Center; University of Southern California, Neurology Cramer, Steven; University of California Los Angeles, Neurology; California Rehabilitation Institute, Director of Research
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Abstract—

Objective. Many patients with subacute stroke rely on the nonparetic arm and leg to propel manual wheelchairs. We designed a bimanual, lever-driven wheelchair (LARA) to promote overground mobility and hemiparetic arm exercise. This study measured the feasibility of using LARA to increase arm movement, achieve mobility, and improve arm motor recovery (clinicaltrials.gov/ct2/show/NCT02830893).

Design. Randomized, assessor-blind, controlled trial.

Setting. Two inpatient rehabilitation facilities.

Subjects. Nineteen patients with subacute stroke (one week to two months post-stroke) received 30 minutes extra arm movement practice daily, while admitted to inpatient rehabilitation (*n*=10) or before enrollment in outpatient therapy (*n*=9).

Interventions. Patients were randomized to train with the LARA wheelchair (*n*=11) or conventional exercises with a rehabilitation therapist (*n*=8).

Main measures. Number of arm movements per training session; overground speed; Upper Extremity Fugl-Meyer score at three-month follow-up.

Results. Participants who trained with LARA completed 254 (median) arm movements with the paretic arm each session. For three participants, LARA enabled wheelchair mobility at practical indoor speeds (0.15–0.30 m/s). Fugl-Meyer score increased 19±13 points for patients who trained with LARA compared to 14±7 points with conventional exercises (p=0.32). Secondary measures including shoulder pain and increased tone did not differ between groups. Mixed model analysis found significant interaction between LARA training and treatment duration (p=0.037), informing power analysis for future investigation.

Conclusions. Practising arm movement with a lever-driven wheelchair is a feasible method for increasing arm movement early after stroke. It enabled wheelchair mobility for a subset of patients and shows potential for improving arm motor recovery.

Keywords—Stroke, rehabilitation interventions, upper extremity, mobility, wheelchair.

Introduction

In the early stages after stroke, many patients have poor mobility and undertake little activity with their hemiparetic upper limb. This likely contributes to limited use of their paretic upper limb into the chronic phase of their injury,[1–4] which reduces self-reported quality of life and well-being.[5–7]

Wheelchairs propelled with levers used by both arms have the potential to offer both mobility and arm exercise.[8,9] Such devices could lead to a paradigm shift in wheelchair use in stroke rehabilitation. Currently, wheelchairs are used for ambulation after stroke, but are not typically thought of as a tool for exercise of the hemiparetic arm.[10,11] Rehabilitation therapists typically focus on teaching compensatory manual wheelchair ambulation with the nonparetic arm and leg to achieve wheelchair ambulation. However, this has the tradeoff of encouraging disuse of the paretic arm and may lead to the development of asymmetric muscle tone.[11,12]

LARA (Lever-Actuated Rehabilitation and Ambulation) is a bimanual lever-driven wheelchair configured so that the paretic arm contributes to propulsion.[8,13] Pilot testing with a precursor device called RAE (the Resonating Arm Exerciser), which utilized the same lever configuration as LARA, showed that individuals with severe arm impairment in the chronic stage of stroke can pump a lever attached to the wheels of a wheelchair with their hemiparetic arm, rolling forward and backward, and that repeated pumping of these levers leads to therapeutic benefit.[14] We tested RAE in a home-based randomized control trial where independent training with RAE (~500 repetitions per hour) was found to be feasible and to significantly reduce arm impairment in individuals with chronic stroke, without increasing pain or tone.[15]

Motivated by these positive results, we adapted the principles of RAE, which permitted only stationary exercise, into a fully mobile, lever-driven wheelchair, LARA.[16] We found that people with severe arm impairment from chronic stroke were able to reliably propel themselves overground, using the mechanically passive assistance of LARA, mostly without using abnormal compensatory shoulder or trunk movements.[8] We then implemented a novel drive system we call "yoked hand clutching"[13] and found that people with severe hemiparesis from chronic stroke could learn, over the course of several training sessions, to coordinate the levers and hand clutch to move forward, turn, and back-up.[9] The question remained whether persons early after a stroke could similarly learn to drive LARA using yoked hand clutching in a subacute rehabilitation setting, and whether such use would have a therapeutic effect on arm impairment.

Here, therefore, we investigated two primary aims, which can inform future clinical research with LARA or similar devices. Our first aim was to determine whether it is feasible to use a bimanual, lever-driven wheelchair to increase a patient's total number of upper extremity practice movements early after stroke and to achieve wheelchair mobility. Our second aim was to test whether adding 30 minutes of daily training with the LARA wheelchair was more effective in improving arm motor recovery than adding a matched amount of conventional exercises, and whether this would lead to any adverse increase in shoulder pain or muscle tone. Barring a significant result, our secondary aim was to estimate the effect size of LARA training to inform a power analysis for a clinical trial. A preliminary analysis of the study results was previously reported in abstract form.[17]

Methods

This study was a randomized, assessor blind, controlled trial, with parallel design and was registered on ClinicalTrials.gov (NCT02830893) as "Efficacy Study of the LARA Wheelchair System for Subacute Stroke Patients". All procedures were approved and overseen by the Institutional Review Boards of the University of California, Irvine (HS# 2016-3304) and Rancho Los Amigos National Rehabilitation Hospital (IRB# 227). This work was supported by grant R44HD082882 from the NIH National Center for Medical Rehabilitation Research.

Clinical Setting, Recruitment, and Randomization

Recruitment took place between June 2017 and May 2018 at the inpatient rehabilitation facilities of the UC Irvine Medical Center and Rancho Los Amigos National Rehabilitation Center. Due to recruitment challenges, the original inclusion criteria were revised to include participants with earlier dates of stroke onset (increased from 4 weeks to 2 months prior) and Fugl-Meyer score (increased upper limit from 29 to 55), and to include individuals discharged from inpatient rehabilitation. Two participants were recruited using the original inclusion criteria. The final inclusion criteria for this study were:

- Age 18 to 80 years at the time of enrollment.
- Stroke onset between 1 week and 2 months prior to enrollment.
- Upper-Extremity Fugl-Meyer[18] $\leq$ 55 (out of 66) at enrollment assessment.
- Concurrently or recently admitted to an inpatient rehabilitation facility but not yet enrolled in outpatient therapy.

The exclusion criteria were:

- Inability to perform the stationary exercise task with LARA (i.e., rocking the lever back and forth with the paretic arm, without engaging the clutch).

- Any deficit in vision, alertness, language, attention, or other cognitive function that interferes with the task.
- Difficulty in understanding or complying with the instructions given by the experimenter.
- Moderate to severe shoulder pain (score ≥ 3 on the 10-point Visual Analog Pain Scale[19]) either at rest or during an active shoulder raise.
- Severely increased tone in paretic upper extremity (score ≥ 3 of 4 on the Modified Ashworth Scale[20]).
- Severe aphasia (score ≥ 2 on question 9 of the NIH Stroke Scale[21]).
- Severe loss of sensation in paretic upper extremity (score < 1 on the Nottingham Sensory Assessment for paretic upper extremity[22]).
- Currently pregnant.

Participants were randomized to train with the LARA wheelchair or conventional exercises with a rehabilitation therapist. The first participant was randomly assigned based on a computerized random number generator, then groups were adaptively balanced with a program that used a deterministic algorithm that reduced differences between mean and standard deviation between groups in both age and Upper-Extremity Fugl-Meyer score; all four were weighted equally. The target sample size of 44 participants was selected based on a predicted effect size of 1.04 to give an 85% chance of observing a significant effect of training ($\alpha = 0.05$), assuming a dropout rate of 20%. This effect size was estimated from the results an study involving rocking chair-based exercise,[23] which was expected to be similar in style and dose to the LARA training protocol used here. As recruitment neared the sample size, the algorithm placed greater weight, $w = \min\{1, (n/42)^2\}$, on balancing group size, where *n* was the number of participants including the one being assigned. The program was operated by a person who had no contact with study

participants. The therapists assessing patients' eligibility received this allocation from the program operator only after fulfillment of complete eligibility criteria was confirmed.

Interventions

Participants in both the LARA and conventional exercise groups received 30 minutes of extra arm movement practice each day while admitted to inpatient rehabilitation or after discharge from inpatient rehabilitation while waiting to be enrolled in outpatient therapy. The inpatients also received their normal rehabilitation therapy, which consisted of 180 minutes per day, five days per week, of physical, occupational, and, as needed, speech therapy. Physical therapy was focused on bed mobility, transfer, gait, balance, and coordination training; occupational therapy on activities of daily living like dressing, feeding, and grooming; and speech therapy on cognitive and memory training and swallowing evaluation. Participants were trained in their respective exercises by a rehabilitation therapist and supervised during all sessions. Training proceeded 5 days per week for 3 weeks, or the duration of each participant's inpatient stay or availability if shorter.

LARA group. The LARA wheelchair used in this study (Figure 1) used yoked hand clutching:[13] each wheel of the chair was actuated by a separate clutch, yet both clutches were controlled simultaneously by a single clutch handle, operated by the user's nonparetic hand. Each clutch consisted of a hydraulic disc brake, which when closed, firmly connected the lever to the wheel (not to be confused with traditional wheelchair brakes, which connect the wheel to the frame). The hydraulic lines of the two clutches were connected, so that squeezing a single clutch handle simultaneously engaged both disk brakes. The LARA wheelchairs used in this study had tailor-made connections to ensure firm fitting between the clutching mechanisms and the manual wheelchair. The wheelchair and its clutching mechanism were kept assembled throughout the study duration. Part of these connections included a set of springs that held the levers in an upright

resting position. These springs also allowed the user to slow the wheelchair simply by squeezing the clutch handle, which would gently pull the levers forward into this spring resistance, preventing the chair from rolling forward any further, since the levers were firmly attached to the wheels when the clutch handle was squeezed.

Pumping both levers in unison resulted in either forward or backward motion, depending on the synchronization of hand clutching, with each pump. Because both clutches were operated simultaneously by a single clutch handle, generally operated by the nonparetic hand, pumping the levers in opposite directions resulted in turning the wheelchair in place, either to the left or right, depending on the synchronization of clutching. These operating dynamics required some active movement of the paretic arm to decouple forward motion from turning toward the paretic side. For more details, see the training videos used for this study, available at: https://www.youtube.com/channel/UCg9J4dMOA-vIfToVYDY-2Ow. In stationary mode, i.e., when clutches were not engaged, interactive videogames could be played by coordinating movement of the levers.[16]

Thus, the LARA wheelchair used in the present study featured two modes of exercise: *1*) playing videogames in a stationary mode using the instrumented levers as joysticks and *2*) ambulating in overground mode by bimanually pumping the levers while engaging the hand clutch, moving in various patterns, including in a circle, in a straight-line, and in figure-of-eight. It was intended that patients might transition from stationary to overground mode as their strength and coordination increased. Therefore, each participant's supervising therapist selected the patient's activities based on the patient's ability and interest. The instructional video demonstrating the operation of LARA in overground mode was played during the first two sessions.

Therapists were instructed to coach participants who propelled LARA not to compensate by using good arm/good leg compensatory wheelchair ambulation. They were instructed to lock the foot rest on the "good side" if needed to block this behavior. Furthermore, if the supervising therapist noticed compensatory forward trunk movement and verbal coaching failed to correct it, they were instructed to install a chest strap to block such behavior. Seat and back cushions were used to promote better upright sitting posture. An in-service was provided to the staff at each rehabilitation unit to train them in the use of LARA, during which the research team demonstrated and instructed staff how to operate and assist patients in and out the LARA wheelchairs.

Conventional exercise group. The other half of the participants performed a matched duration of standard arm exercises for 30 min per day, 5 days per week, for up to 3 weeks, in addition to their regular rehabilitation therapy. This program of standard arm exercises, herein referred to as "conventional exercises", was developed by experienced occupational therapists at the Shirley Ryan AbilityLab. Facilitated by their therapist, the participant followed a booklet that guided them through a series of graded-difficulty, table-supported exercises. These included shoulder and elbow flexion/extension, shoulder abduction/adduction, shoulder internal/external rotation, forearm supination/pronation, wrist flexion/extension, finger and thumb flexion-extension, and a weight bearing exercise for the arm. The patient was instructed to use the muscles of their paretic arm, using the nonparetic arm only as needed for guidance and support. This program is representative of semi-autonomous exercise programs that stroke patients undergo as part of standard of care.[15]

Outcome Measures and Data Collection

The primary clinical outcome measure was change in Upper Extremity Fugl-Meyer score from baseline to three-month follow-up. Secondary outcome measures included the Box and

Blocks Test[24] score; grip strength; shoulder pain; the average score on the Modified Ashworth Scale across shoulder, elbow, wrist, and finger flexors; and time to complete the 10-m Walk Test.[25] Grip strength was measured as the average between power grip and pinch grip strengths, each normalized with respect to the nonparetic hand. Pain was measured using the Visual Analog Pain Scale, a validated measure for pain intensity.[19] Participants were asked to mark their level of pain on a line, with "0" on one end representing no pain, and "10" on the other end representing severe pain. Participants identified their pain level twice, once when their arm was at rest, and once after completing an active shoulder raise movement. Their marks in response to each were measured and the average value of these measurements was reported on a scale between 0 and 10. Each of these assessments was conducted at each evaluation visit: baseline (BL), post-intervention (PI), and three-month follow-up (FU). Evaluators were blinded to treatment group, with each participant receiving all three assessments from the same evaluator.

We also quantified feasibility of exercise with LARA by measuring the number of arm movements that participants completed with LARA during each training session and their speed of overground mobility. To monitor their number of arm movements, we developed an application that counts the number of times the movement of each lever changed directions, based on measurements from the inertial measurement units attached to the levers. To protect against over-counting, an averaging filter and a minimum speed threshold were used to ensure that neither small reversals nor short stop-and-start movements were counted as distinct arm movements. Therefore, a full forward and backward pump of the lever was counted as two arm movements, even if the movement was not continuous. To measure their overground speed, this system recorded the time required to drive the chair three meters, from which mean velocity was calculated. The therapist

who guided the conventional exercise group also recorded on a written log sheet the amount of time each participant spent exercising.

Data Analysis

We hypothesized that adding 30 min of daily training with the LARA wheelchair is more effective than adding a matched duration of conventional exercises in relation to arm motor recovery. We assessed our primary outcome measure, change in Upper-Extremity Fugl-Meyer score from baseline to three-month follow-up, and all secondary outcomes, using Students' independent, two-sided t-test with $\alpha=0.05$. No correction was made for multiple comparisons given the pilot nature of this study. Factors relating to recruitment and protocol limited the power of this study. We therefore conducted a power analysis on the acquired data to inform recruitment of a future clinical trial. This included a linear mixed model analysis to estimate the effect size of LARA training as a function of training duration (this analysis is detailed in the online supplement).

Results

Participant recruitment and characteristics: Details of recruitment and allocation are shown in the study flow diagram (Figure 2). The study was stopped before recruiting the planned 44 participants, due to running its planned time and budgetary course. There were minimal differences between groups in age, stroke severity, arm impairment, or time post-stroke at baseline assessment (Table 1). No adverse events were reported during the study.

Intervention dose: Participants in the LARA group completed a mean (SD) of 5.7 (3.9) exercise sessions, each of which lasted 34.6 (9.2) minutes. Participants in the conventional exercise group completed 6.3 (3.4) exercise sessions that lasted 30.4 (2.2) minutes. The sensor application

did not collect data for two participants due to a wireless communication error. The remaining participants in the LARA group completed a median (IQR) of 254 (202 to 454) arm movements with their paretic arm each session. Arm movements were not counted for the conventional exercise group, only the duration of exercise completed.

Assessment and intervention timing: The intervention began between 1 to 22 days after the baseline assessment, with a median (IQR) of 3 days (2 to 6). The post-intervention assessment took place between 0 (same day) and 27 days after the last training session of the intervention, with a median (IQR) of 3 days (1 to 6). The follow-up assessment took place between 53 to 99 days after the post-intervention assessment, with a median (IQR) of 86 days (70 to 94).

Wheelchair ambulation: By the end of training, 25% (n = 3) of the participants in the LARA group became skillful at overground wheelchair ambulation with LARA, achieving top speeds of 0.15, 0.25 and 0.30 m/s (averaged across their last two training sessions).

Primary outcome: The primary clinical outcome measure, the Upper Extremity Fugl-Meyer score, increased between baseline and three-month follow-up more for the LARA training group compared to the conventional therapy group (Figure 3, Table 2), but this difference was not statistically significant. The difference between groups was more pronounced at the post-intervention assessment, but this too was not significant.

Secondary outcomes: No secondary clinical outcome measures showed a significant difference between treatment groups (Table 2). Of particular note, the differences in shoulder pain and increased muscle tone between groups was minimal.

Power analysis: This study's statistical power was limited by both recruitment and the number of training sessions being lower than planned. Therefore, we conducted a linear mixed model analysis as part of a post hoc power analysis to inform the recruitment and design for a

future clinical study (full results in the online supplement). This analysis found that the effect of treatment duration on Upper Extremity Fugl-Meyer score was significantly moderated by treatment group, with a greater increase for the LARA training group ($p = 0.037$). The model predicts that 300 minutes of additional LARA training would increase Upper Extremity Fugl-Meyer score at follow-up by 8.4 points more than the same duration conventional therapy. Based on this figure, a study could achieve a power of 0.8 at $\alpha=0.05$ by recruiting 26 participants for each treatment group and ensuring that participants in each group receive an average of 10 sessions with 30 minutes of training each.

Discussion

The results of this pilot study indicate that practicing arm movement with a lever-drive wheelchair is a feasible method for increasing arm movement early after stroke without increasing shoulder pain or tone. Using LARA for overground ambulation around the rehabilitation unit also appears to be feasible for roughly a quarter of patients with subacute stroke who have severe arm impairment and do not have other complex comorbidities, such cognitive impairment. We found that these patients achieved practical indoor speeds between 0.15 and 0.25 m/s. For reference, manual wheelchair use ordinarily consists of median bouts that last 21 s at 0.43 m/s.[26] LARA training shows potential for improving arm motor recovery compared to a matched duration of conventional exercise, but this needs to be tested in a larger study.

The arm movements used to operate LARA in both the stationary and overground modes are reminiscent of the simple repetitive arm movements studied by Feys et al., who found that operating a rocking chair with the paretic arm led to substantial improvements in arm function among patients with subacute stroke after 30 sessions,[27] improvements that were sustained at 5-

year follow-up.[23] LARA training provides a similarly high dose of arm movement during a 30-minute training session. Specifically, the dose of 202 to 454 arm movements (IQR), measured during each session of LARA training, placed some participants above the threshold of 300 movements per session, below which Lang et al. found dose-dependence to be lacking.[28] For comparison, the most recent clinical trials with the BATRAC and Bi-manu-track, two devices that facilitate repetitive, bilateral exercise, did not show superiority to a matched duration of conventional exercises in subacute stroke.[29,30] But in an earlier trial, when training with the Bi-manu-track did outperform conventional exercises, it also managed to facilitate an order of magnitude increase in the number of arm movements that patients performed.[31] Also of note, compared to these past protocols of simple unimanual and bimanual movements, arm exercise with LARA likely puts greater demands on coordination and cognition, whether through gameplay or navigation during propulsion.

Three (25%) of the participants in this study achieved overground wheelchair ambulation, which suggests that some patients might be able to use LARA as a mobility device. Among those who did not achieve this ambulation, it appeared that several struggled to coordinate the timing of squeezing the clutch handle with their nonparetic hand while simultaneously pumping the lever with their paretic arm. Often they activated the clutch too late in the pump to achieve meaningful propulsion, or they did not deactivate the clutch before pulling their paretic arm back, thereby stopping or even reversing the chair's motion. We believe it is possible to increase the fraction who achieve mobility by simplifying the propulsion mechanism. For example, we are working on techniques to circumvent the need for yoked clutching, which can be cognitively challenging to learn.

Although overground wheelchair ambulation was not feasible for the majority of patients who participated in this study, the stationary video gaming mode of LARA was feasible for all participants, was engaging, and appears to have been beneficial to patients on its own. This suggests that implementation of wheelchair-based devices like LARA into subacute stroke treatment should incorporate such a stationary exercise mode, and not solely focus on directly promoting ambulation. We note that overground ambulation with LARA may also be more feasible later during recovery. Indeed, we found in a prior pilot study that a high fraction of subjects with chronic stroke were able to learn to propel LARA with yoked clutching.[9]

A strength of this study was the similar duration of experimental treatment received by both treatment groups. Limitations of this study included its smaller than intended sample size, the lower than intended dose of experimental treatment received by most participants, and imbalance in combinations of baseline characteristics between treatment groups. Mixed model analysis was used to control for these covariates and suggested a significant benefit of LARA training despite the underpowered sample size. Future studies should budget for the recruitment challenges observed here, anticipating that ~12% of patients assessed for eligibility will complete the study. Another limitation is that this study was not able to separate the benefits of stationary and overground modes.

Mixed model and power analyses suggest that an appropriately powered (n=52) clinical study with LARA can be used to validate these promising preliminary findings. This analysis assumes that participants in such a study would complete two weeks of daily training with LARA, which will require logistic improvements over the present study. Should these results be validated, future research could then seek to optimize therapeutic wheelchair technology, including identifying the user population who possess the residual neural resources needed to realize the

greatest benefit from such training,[32] and to develop pragmatic protocols for stationary and overground use,[14,15] including potentially simplifying the propulsion mechanism so more users can achieve wheelchair mobility.

Clinical Message

- Using a lever-driven wheelchair for additional arm training during inpatient rehabilitation was feasible to help patients undertake ~250 arm movements per 30-minute session.
- Three of 12 patients achieved skillful overground ambulation in the chair at speeds that were viable for navigating an inpatient rehabilitation facility.
- The additional arm activity patients achieved tended to reduce arm impairment immediately after the intervention and at three-month follow-up. A larger clinical study (estimated sample of n=52) is needed to validate the benefits of training with LARA on arm impairment reduction.

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Contribution of Authors

Order of contribution to each part of the project is listed by author order. BWS, JLP, DKZ, DJR, and SCC conceived the present project. DJR, SS, ST, and SCC managed the project. BWS,

DKZ, and DJR conceived of the experimental device. JLP and DKZ prepared and maintained experimental hardware and software for the project. VC, JLP and DKZ provided in-service training for experimental device and protocol. VC and ST recruited and screened experimental participants. CC conducted clinical experiments and assessment. BWS performed the formal analysis. BWS and JLP wrote the original draft. All authors reviewed and edited the manuscript.

Competing Interests

DKZ and DJR are co-founders of and hold equity in Flint Rehabilitation Devices, a company that is commercializing rehabilitation technology. DKZ is currently employed at Flint, and DJR has received payment for consulting from Flint. DJR holds equity in Hocoma, a manufacturer of rehabilitation technology. The terms of DJR's interests have been reviewed by the U.C. Irvine Conflict of Interest committee. Dr. Cramer serves as a consultant for Abbvie, Constant Therapeutics, MicroTransponder, Neurolutions, Regenera, SanBio, Stemedica, Fujifilm Toyama Chemical Co., Biogen, and TRCare.

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Table 1. Baseline characteristics.

	LARA (*n* = 11) N (%)	Conventional (*n* = 8) N (%)	*p*-value
Age (Years)			
Mean (SD)	52.1 (7.9)	52.6 (9.5)	0.91[a]
Range	37–64	40–67	
Sex			
Female	2 (18)	1 (12)	0.73[b]
Male	9 (82)	7 (88)	[c]
Paretic Side			
Right	7 (64)	3 (38)	0.26[b]
Left	4 (36)	5 (62)	[c]
Type of stroke			
Ischemic	6 (55)	5 (62)	0.73[b]
Hemorrhagic	5 (45)	3 (38)	[c]
Stroke risk factors			
Hypertension	10 (91)	6 (75)	0.35[b]
Diabetes mellitus	4 (36)	4 (50)	0.56[b]
Coronary artery disease	0 (0)	2 (25)	0.080[b]
Smoking	1 (9)	1 (12)	0.81[b]
Alcoholism	1 (9)	1 (12)	0.81[b]
Time post-stroke (days)			
Mean (SD)	26.5 (19.2)	25.1 (11.5)	0.85[a]
Range	7–68	9–37	
Treatment Stage			
Inpatient	6 (55)	4 (50)	0.84[b]
Discharged	5 (45)	4 (50)	[c]
Treatment Duration (Sessions)			
Mean (SD)	5.7 (3.9)	6.3 (3.4)	0.73[a]
Range	1–14	3–14	
Severity (National Institute of Health Stroke Scale)			
Mild (0–7)	9 (82)	8 (100)	0.20[b]
Moderate (8–16)	2 (18)	0 (0)	[c]
Severe (>16)	0 (0)	0 (0)	[d]
Upper Extremity Fugl-Meyer			
Mean (SD)	28.5 (11.6)	27.4 (14.7)	0.86[a]
Range	12–48	10–45	

SD=Standard deviation.

[a]Analyzed by Student independent t-test, two-sided. [b]Analyzed by two sample z-test. [c]Same as above. [d]Undefined.

Table 2. Clinical outcome measures.

	LARA (n = 11) Mean (SD)	Conventional (n = 8) Mean (SD)	*Difference (95% Conf. Int.)*	*p*-value
Arm Impairment (Upper-Extremity Fugl-Meyer)				
Baseline (BL)	28.5 (11.6)	27.4 (14.7)		
Post-Intervention (PI)	42.7 (15.5)	35.3 (15.6)	[-7.4, 22.7]	0.32[a]
3-month Follow-up (FU)	47.4 (15.5)	41.5 (20.1)	[-11.3, 23.1]	0.50[a]
Change in score (PI-BL)	14.2 (10.8)	7.9 (3.8)	[-2.1, 14.7]	0.10[a]
Change in score (FU-BL)	18.8 (12.5)	14.1 (7.4)	[-5.8, 15.2]	0.32[a]
Change in score (FU-PI)	4.6 (5.0)	6.3 (6.6)	[-7.2, 4.0]	0.57[a]
Dexterity (Box and Blocks Test)[b]				
Baseline	8.5 (10.8)	11.9 (13.6)		
Post-Intervention	23.5 (19.2)	22.1 (22.7)	[-19.0, 21.6]	0.90[a]
3-month Follow-up	32.1 (19.4)	30.8 (24.4)	[-19.9, 22.6]	0.90[a]
Grip Strength (%)[c]				
Baseline	14.4 (19.9)	16.4 (20.6)		
Post-Intervention	34.9 (26.1)	29.8 (31.9)	[-23.0, 33.2]	0.72[a]
3-month Follow-up	53.4 (31.8)	45.8 (44.6)	[-29.2, 44.6]	0.68[a]
Increased Tone (Modified Ashworth Scale)[d]				
Baseline	0.64 (0.64)	0.56 (0.61)		
Post-Intervention	0.47 (0.56)	0.77 (0.80)	[-0.95, 0.36]	0.39[a]
3-month Follow-up	0.61 (0.72)	0.96 (1.37)	[-1.37, 0.67]	0.53[a]
Shoulder Pain (Visual Analog Pain Scale)[e]				
Baseline	2.1 (2.6)	2.1 (3.1)		
Post-Intervention	1.3 (1.5)	1.1 (1.4)	[-1.28, 1.58]	0.83[a]
3-month Follow-up	2.2 (2.0)	1.8 (1.9)	[-1.44, 2.40]	0.60[a]
10-m Walk Time (s)[f]				
Baseline	18.8 (9.7)	23.4 (9.1)		
Post-Intervention	15.2 (7.5)	14.4 (5.0)	[-7.1, 10.4]	0.81[a]
3-month Follow-up	11.8 (4.4)	11.8 (3.7)	[-3.7, 3.8]	0.97[a]

SD=Standard deviation.

[a]Analyzed by Student independent t-test, two-sided. [b]Reported for paretic side. [c]Average between grasp and pinch strength, each expressed as ratio of strength with paretic hand to that with nonparetic hand. [d]Average of flexion scores for shoulder, elbow, wrist, and finger; scores were either 1, 1+, 2, 3 or 4, with scores of 1+ assigned the value of 1.5. [e]Average of VAS-P reported when arm at rest and during an active shoulder raise. [f]Including only participants in LARA (n = 6) and Conventional (n = 7) who could complete the 10-m walk at Baseline.

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Figure 1. LARA is a novel lever drive wheelchair that has two modes of exercise: (1) playing a bimanual videogame (top right – the goal is to keep the spaceship between the cones by steering it by pumping the left and right levers) or unimanual videogame (bottom right – the goal is to raise and lower the balloon by pumping the paretic-arm lever faster of slower, to collect the gold coins) in a stationary mode using the instrumented levers as a joystick and (2) ambulating overground by bimanually propelling the wheelchair using the levers. The hand clutch (top left) is yoked to disk brakes on both wheels and activated during overground ambulation. It functions akin to a hand grasping the pushrim and provides maneuverability over level ground.

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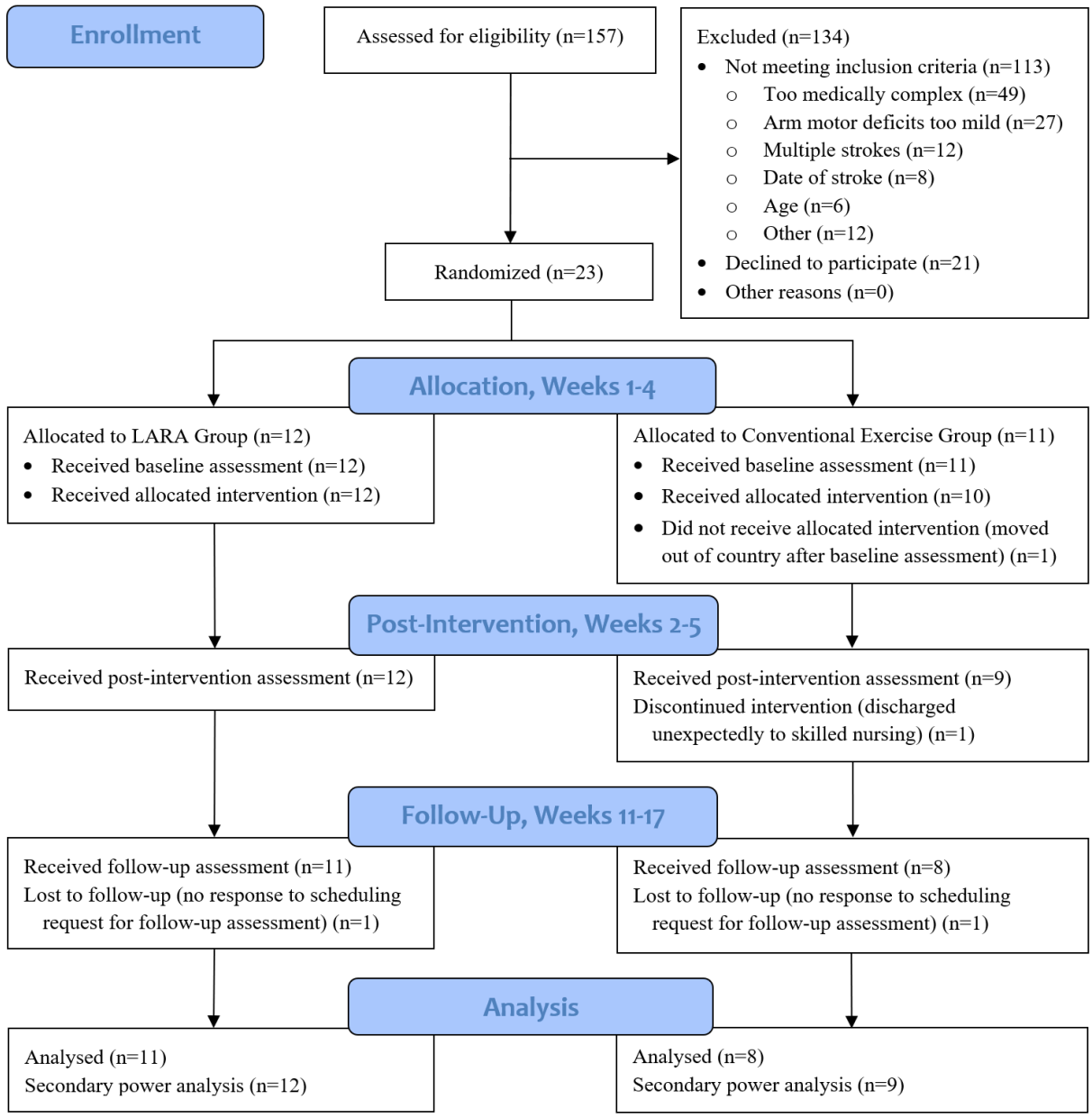

Figure 2. Study recruitment, retention, and flow diagram.

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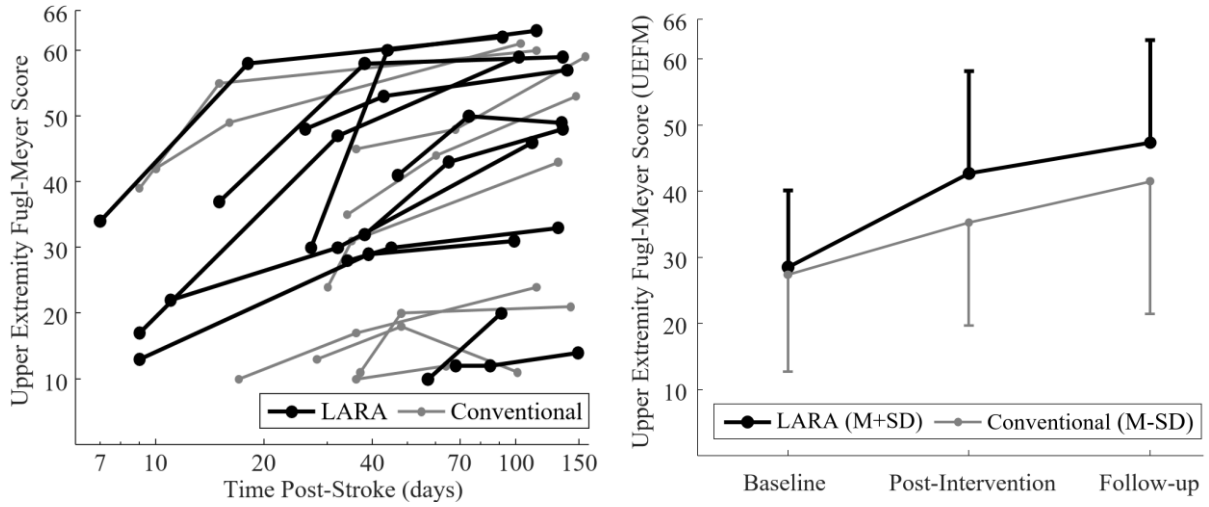

Figure 3. Arm impairment of each participant at each assessment (baseline, post-intervention, and three-month follow-up). The Upper-Extremity Fugl-Meyer score (max 66) is the combination of 33 simple upper extremity movements, each scored 0 (no movement), 1 (some movement), or 2 (full movement). Time post-stroke is presented on a logarithmic scale, consistent with how this factor was used during the mixed-model power analysis (see the online supplement).

Online Supplement: Mixed Model and Power Analyses

This study's primary analysis, via Students' independent, two-sided t-tests, was found to have limited power due to *1*) an uneven distribution of participants across the covariate space of Time Post-Stroke and Baseline Upper-Extremity Fugl-Meyer (Figure 3 in main article), even though these covariates were individually balanced during allocation; and *2*) a sizable variability in Treatment Duration across participants (199 ± 143 minutes). These limitations would also diminish the predictive power of any effect size estimated directly from the population mean and standard deviation, without controlling for these covariates. Therefore, a mixed model analysis was used to make a stronger estimate of the effect size of LARA training. Mixed model analysis is robust to data with multiple covariates and also allows for the inclusion of participants with missing data,[1] i.e., the two who dropped out before three-month follow-up.

We conducted linear mixed model analysis using SPSS Statistics Version 24 (IBM, USA). The linear mixed model predicted variation in the dependent variable, Upper-Extremity Fugl-Meyer at each assessment, in terms of four fixed effects and two random effects. Fixed effects included "Treatment Condition" (LARA or conventional training), "Time Post-Stroke" at which the assessment occurred (days, logarithmic transform), "Treatment Duration" i.e. total duration of extra LARA or conventional exercises received prior to that assessment (minutes, square root transform), and the interaction between Treatment Condition and Treatment Duration. The effectiveness of LARA training at reducing arm impairment was evaluated based on the significance of this interaction term. The model handled the repeated measures design using two random factors: an intercept (i.e., subject-specific baseline Upper-Extremity Fugl-Meyer) and a

slope for Time Post-Stroke (i.e., subject-specific rate of spontaneous recovery[2]), with a scaled identity covariance structure.

Model Selection

We followed the stepwise model selection process detailed by Seltman,[3] which provides a guided manner for evaluating the predictive quality of each factor and covariate. The model was refined using the penalized likelihood method based on the Bayesian information criterion (BIC), which considers both model complexity and sample population size to avoid over-fitting to small sample population (e.g. n=20). Initially all main effects and single interactions of two factors (Treatment Condition and Evaluation Stage) and three covariates (Time Post-Stroke, Treatment Duration, and Baseline Upper-Extremity Fugl-Meyer) were included, as were two random effects (an intercept and Time Post-Stroke). "Evaluation Stage" had three levels: baseline, post-intervention, and follow-up. "Baseline Upper-Extremity Fugl-Meyer" was each participant's Upper-Extremity Fugl-Meyer at the baseline assessment.

The model selection process begins with the over-parameterized full model. It then iteratively simplifies the model by removing one fixed effect at a time until the BIC increased instead of decreasing following that term's removal. Minimizing BIC indicates that the model has arrived at an optimal balance between model fit and model complexity. Main effects were only removed if all their interaction terms had been previously removed. Because it is scientifically problematic to model correlation between Upper-Extremity Fugl-Meyer at baseline and later Upper-Extremity Fugl-Meyer assessments,[2,4] the main effect of Baseline Upper-Extremity Fugl-Meyer was removed as soon as all its interactions had been removed, even though this increased BIC. Per guidelines by Seltman,[3] BIC was estimated using standard maximum likelihood because only fixed effects were considered for removal. Restricted maximum likelihood was used to

calculate significance levels for the final model and to confirm that the selected random effects and covariance structure led to the model that best fit the data.

Mixed Model Results

Model selection determined that the interaction between Treatment Duration and Treatment Condition (i.e., the cumulative impact of LARA training relative to conventional therapy) and Time Post-Stroke (i.e., a proxy for spontaneous recovery) were sufficient to explain the differences in Upper-Extremity Fugl-Meyer measured across participants at baseline, post-intervention, and three-month follow-up assessments (Table S1). This suggests that the impact of LARA training was maintained at follow-up, since model selection rejected any term that could account for an attenuation of this effect between post-intervention and follow-up. For instance, the model's fit to the data was reduced by including a term for the interaction of Treatment Condition with Evaluation Stage (the best such model increased BIC by 10.0, a sizable reduction in model fitness[3]). The model's fit was also reduced by including the interaction between Treatment Duration and Time Post-Stroke or any interactions that included Baseline Upper-Extremity Fugl-Meyer. This suggests that improvements in Upper-Extremity Fugl-Meyer were independent of both treatment timing and initial impairment, and stacked with the improvements associated with spontaneous recovery.

The final mixed model (Table S2) identified a significant difference between the effects of LARA training and conventional exercises on Upper-Extremity Fugl-Meyer score. Specifically, there was a significant interaction effect between Treatment Condition and Treatment Duration ($p = 0.037$). Extra treatment in the LARA condition led to greater increases in Upper-Extremity Fugl-Meyer relative to a matched duration of conventional exercises, at a rate that was greater by 0.48 points per root-minute of additional treatment (0.03–0.94, 95% CI). Based on this term, the model

predicts that adding 30 minutes of daily LARA training, for 10 days, anytime during early stroke therapy, can be expected to increase Upper-Extremity Fugl-Meyer score by 8.4 ± 3.9 (SE) points on average relative to adding the same duration of conventional exercises.

Power Analysis

To design an appropriately powered randomized controlled trial to validate the preliminary findings of this feasibility study, we conducted a power analysis based on the mixed model results. We designed for an 80% chance of achieving a Type-1 error rate of $\alpha=0.05$. Effect size was calculated based on the 8.4-point improvement predicted by the mixed model (for 10 sessions of LARA training, 30 minutes each, compared to an equal duration of conventional therapy) and the combined standard deviation of 10.7 points measured in this study across participants in both experimental conditions. This analysis predicted that an appropriately powered study could be achieved with 52 participants, 26 in each treatment condition. Because this power analysis is based on 10 sessions of experimental treatment it is important that participants completed the planned number of training sessions.

References

1. Molenberghs G, Verbeke G. A review on linear mixed models for longitudinal data, possibly subject to dropout. *Stat Model* 2001; 1: 235–269.
2. Krakauer JW, Marshall RS. The proportional recovery rule for stroke revisited. *Annals of Neurology*. Epub ahead of print 2015. DOI: 10.1002/ana.24537.
3. Seltman HJ. Chapter 15 Mixed Models. In: *Experimental Design And Analysis*. 2015, pp. 357–378.
4. Hope TMH, Friston K, Price CJ, et al. Recovery after stroke: Not so proportional after all? *Brain* 2019; 142: 15–22.

Table S1. Linear mixed model terms and significance.

Model Term	*df 1*	*df 2*	*F*	*p-value*
Intercept	1	42.7	20.1	<0.0005
Treatment Condition	1	43.9	0.003	0.956
ln{Time Post-Stroke}	1	58.0	5.47	0.023
{Treatment Duration}$^{0.5}$	1	37.3	22.7	<0.0005
Treatment Condition × *{Treatment Duration}*$^{0.5}$	1	48.7	4.61	0.037

Dependent Variable: Upper-Extremity Fugl-Meyer

Table S2. Estimates of Fixed Effects.

Model Term	*Est.*	*SEM*	*df*	*t*	*p-value*	*95% Conf. Int.*	
Intercept	16.9	4.37	53.9	3.87	<0.0005	8.13	25.6
[Treatment Condition = Conv.]	0.269	4.85	43.9	0.055	0.956	-9.52	10.1
[Treatment Condition = LARA]	0[a]	0[a]					
ln{Time Post-Stroke}	3.26	1.40	58.0	2.34	0.023	0.47	6.06
{Treatment Duration}$^{0.5}$	0.888	0.184	44.2	4.83	<0.0005	0.52	1.26
[Treatment Condition = Conv.] × *{Treatment Duration}*$^{0.5}$	-0.483	0.225	48.7	-2.15	0.037	-0.936	-0.031
[Treatment Condition = LARA] × *{Treatment Duration}*$^{0.5}$	0[a]	0[a]					

[a]This is the default value of the fixed effect; this behavior is modelled by other terms, e.g. Intercept, Treatment Duration.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Title Page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	1-2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3-5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	3
Participants	4a	Eligibility criteria for participants	3-4
	4b	Settings and locations where the data were collected	3
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	9
Sample size	7a	How sample size was determined	4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	9
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4-5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4-5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4-5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4-5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	5
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9, Suppl.
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7,21
	13b	For each group, losses and exclusions after randomisation, together with reasons	21
Recruitment	14a	Dates defining the periods of recruitment and follow-up	3,21
	14b	Why the trial ended or was stopped	9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	18
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	21
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	19
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10-11, Suppl.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	9
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11-14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-14
Other information			
Registration	23		Abstract, 3
Protocol	24	Registration number and name of trial registry	Abstract, 3
Funding	25	Where the full trial protocol can be accessed, if available	3,15
		Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.