Journal of the American Heart Association

ORIGINAL RESEARCH

Randomized Trial of Combined Aerobic, Resistance, and Cognitive Training to Improve Recovery From Stroke: Feasibility and Safety

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BACKGROUND: Physical exercise and cognitive training have been recommended to improve cognitive outcomes poststroke, but a multifaceted strategy including aerobic, resistance, and cognitive training to facilitate poststroke recovery has not been investigated. We aimed to assess the feasibility, adherence, and safety of a combined aerobic, resistance, and cognitive training intervention (CARET+CTI) after stroke.

METHODS AND RESULTS: We prospectively randomized patients presenting with recent stroke to a comparison of a supervised 12-week CARET+CTI program and a control group receiving sham CARET+CTI. Participants were scheduled for 3 weekly CARET and CTI sessions. All participants underwent pre- and postintervention assessments of strength, endurance, and cognition. The primary outcomes were feasibility and adherence, defined as the ratio of scheduled and observed visits, and safety. We enrolled 131 participants, of whom 37 withdrew from the study. There were 17 (20%) withdrawals in the CARET+CTI and 20 (44%) in the control group. The observed-over-expected visit ratio was significantly higher in the intervention than in the control group (0.74±0.30 versus 0.54±0.38; P=0.003). A total of 99 adverse events were reported by 59 participants, none of which were serious and related to the intervention. Greater gains in physical, cognitive, and mood outcomes were found in the CARET+CTI group than in the control group, but were not statistically significant after adjustments.

CONCLUSIONS: A CARET+CTI intervention, after stroke, is safe, feasible, and has satisfactory participant adherence over 12 weeks.

REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT02272426.

Key Words: cognitive training ■ exercise ■ randomized clinical trial ■ stroke recovery

Physical exercise and cognitive training have been cited by the National Academy of Medicine as promising interventions to improve outcomes among those with age-related cognitive decline.[1] Whether these interventions can improve outcomes after stroke is unknown. Enhancing recovery from stroke, beyond what current rehabilitative services can offer, remains an unmet clinical need. Physical and cognitive impairments make the resumption of previous activities difficult or

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This work was presented as an abstract at the International Stroke Conference, February 6 to 8, 2019, in Honolulu, HI.

Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015377

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Three months of combined aerobic, resistance and cognitive training is safe and tolerable for recent stroke patients.

What Are the Clinical Implications?

- Physical exercise and cognitive training in patients with recent stroke may lead to gains in strength, endurance, cognition and overall quality of life.

Nonstandard Abbreviations and Acronyms

AE	adverse event
CARET	combined aerobic and resistance training
CTI	cognitive training intervention

impossible for many. Attempts to augment stroke recovery pharmacologically have been unsuccessful, and efforts to improve recovery through aerobic or resistance exercise training have either shown modest or only short-lasting benefits.[2] Similarly, the effects of poststroke cognitive training interventions (CTI), particularly to stimulate cognitive recovery, remain uncertain.[3] While a few studies have combined aerobic and resistance exercise training (CARET) to promote recovery, a multifaceted strategy combining aerobic, resistance, and cognitive training to improve stroke outcome has not been thoroughly explored. Given the substantial physical and cognitive impairments following stroke, it is uncertain whether patients can safely adhere to such a demanding intervention. It was therefore our objective to examine the feasibility, adherence, and safety of a supervised, CARET plus CTI program after stroke. Our hypothesis was that this multifaceted intervention was safe and feasible and would lead to improved cognitive outcome.

METHODS

We prospectively randomized patients with stroke to a comparison of a supervised 12-week CARET+CTI, and a control group receiving sham CARET+CTI. Participants were recruited from outpatient clinics and screening hospital discharge logs. Inclusion criteria were stroke within 1 year, age >18 years, modified Ranking scale ≤3, and less than ideal physical activity for at least 3 months before enrollment (defined as <75 minutes of vigorous or 150 minutes of moderate activity per week). We excluded subjects with neurodegenerative diseases and those with unstable medical and psychiatric conditions, which would preclude engaging in physical activity. The study originally included a third, CARET-only arm, but because of slow enrollment, we discontinued enrollment into the CARET-only arm, using simple randomization, and assigned subjects 2:1 to CARET+CTI versus the sham intervention. At that time, 53 participants had been enrolled. The 19 participants who were randomized to the CARET-only arm were subsequently analyzed together with the CARET+CTI arm. The study was approved by the institutional review board at the University of Miami. All participants gave written informed consent to participate in the study. We used the National Institute of Neurological Disorders and Stroke Common Data Elements (http://www.commondataelements.ninds.nih.gov/). Study data are available from the corresponding author upon reasonable request.

Intervention

Participants were scheduled for 3 weekly 40 to 60 minutes CARET and 40 minutes CTI sessions. We allowed for some variability in the duration of the sessions at the onset of the study, depending on participants' familiarity with equipment and need for instruction of technique. CTI was done after physical exercise. The intervention was done at the UHealth Fitness & Wellness Center, a wellness facility with state-of-the-art aerobic and strength training equipment at the University of Miami. All sessions were supervised by trained personnel who assisted with physical and computer-based cognitive exercises. The same personnel also assessed physical and cognitive outcome. Although outcome assessments were not blinded, every effort was made to have these assessments done by personnel not involved in the training part for a participant. Participants were blinded to group allocation.

Combined Aerobic and Resistance Training

Stationary treadmill or bicycle ergometer (sitting or recumbent) were used for aerobic training. Strength training included core exercises (back extension and abdominal crunches) and 10 resistance exercises on stacked-weight machines (leg press, leg extension, leg curl, chest press, lat pull, shoulder press, seated row, triceps press, biceps curl, and chest fly). Exercises were modified to accommodate varying levels of disability. We always tried to achieve the

same movement for both the affected and nonaffected side by providing a passive or active support or lower resistance for the affected side. The exercise program consisted of 1 different weekly sessions, lasting ≈40 to 60 minutes: (1) session 1 consisted of 20 minutes of aerobic training followed by resistance training (10 exercises of 1–2 sets of 8–15 repetitions); (2) session 2 stressed aerobic exercise training (35 minutes) followed by 20 minutes of core strength exercises; and (3) session 3 consisted of resistance training only (10 exercises of 2–3 sets with 8–15 repetitions), after a 5-minute aerobic warm-up. The starting training intensities were 50% to 55% of the individual's estimated maximum heart rate for aerobic exercise and were gradually increased to 65% as tolerated. Estimated heart rate was determined based on the 220–age formula (eg, for 60%=220–age×0.60). During the study, weights were adjusted so that muscle failure would occur during a set between 8 and 15 repetitions.

Cognitive Training Intervention

The CTI was designed to target auditory and visual attention as well as memory, working memory, processing speed, and executive function. These are cognitive domains particularly affected after stroke.[4] CTI was done for 40 minutes, 3 times a week, using an adaptive computerized platform from Brain Fitness Program, Posit Science, San Francisco, CA. Each session consisted of four 10-minute training tasks targeting attention, memory, psychomotor speed, and working memory (For additional methods see Data S1 and Table S1).[5–7] Participants were instructed on how to complete the cognitive training exercises and study personnel monitored satisfactory progress.

Control Group

All participants randomized to the control group underwent a sham CARET and CTI. The sham CARET intervention involved supervised training of mild stretching and range-of-motion exercises, for three 40-minute sessions a week. The sham cognitive intervention involved computer games such as hangman, anagrams, and word search for 40 minutes three times weekly.

Baseline Evaluations

Sociodemographics, vascular risk factors, and stroke severity, mechanism, and location were collected at baseline. All subjects underwent a standardized assessment of physical strength, mobility, cardiovascular fitness, and cognition at baseline and at the end of the study intervention.

Primary Outcomes

The primary outcomes were feasibility and adherence to the 12-week intervention and safety. We recorded the number of visits attended per week and any adverse events (AE). Our hypothesis was that this multifaceted intervention was feasible with adherence rates and a safety profile comparable to or better than the control group. During the 12-week intervention phase, participants were expected to complete 36 training sessions. For all participants we calculated the ratio of observed/expected (scheduled) visits. Feasibility and adherence were defined as demonstrating that the ratio of observed/expected visits in the intervention group was within −0.5 SD of the control group. All AE were recorded and their relationship to the intervention was adjudicated to assess safety. Out hypothesis was that serious AE would not differ between the groups. We assessed mood, cognitive performance, and physical assessments at baseline, 3 months, and 6 months after the start of intervention. We here report only on 3-month outcomes.

Secondary Outcomes

Mood and Cognitive Assessments

The principal secondary outcome was global cognition, assessed with the Montreal Cognitive Assessment (MoCA) at 3 months. Our hypothesis was that the intervention would lead to improvements in cognition. The study was powered to detect some cognitive improvement. A total sample size of 120 allowed us to detect a medium Cohen effect size of 0.25 ($\sigma m/\sigma$, σm is SD of the group means, σ is the common SD within a group) on MoCA with 85% power for an intent-to-treat analysis. In practical terms, a medium Cohen effect size of 0.25 corresponds to a mean MoCA score of 22.5 for the control group and 25.5 for the CARET+CTI group with σ=4.25.

Other secondary cognitive outcomes included multiple tests measuring working memory, processing speed, verbal/visual learning and memory, and executive function with the Hopkins Verbal Learning Test Revised, Hopkins Verbal Learning Test Revised Delayed Recall, Grooved Pegboard, Stroop Delis Kaplan Executive Function Test, WAIS-IV Coding Digit Symbol Substitution Test, Brief Visuospatial Memory Test-R, Brief Visuospatial Memory Test-R Delayed Recall Digit Span Backwards, and the CogState Brief Battery. All participants completed questionnaires regarding mood (Center of Epidemiological Studies—Depression Scale) and quality of life (Stroke Impact Scale).

Physical Assessments

Physical strength and mobility were examined with the Timed "Up & Go" test and 15 Meters Walk Speed.

The 6-Minute Walk test was used as a measure of cardiovascular fitness.[8] Participants could use foot-ankle orthoses or assistive devices such as walkers or canes while performing these assessments. These gait performance tests have been found to be highly reliable in stroke survivors.[9] In addition, we included the 30-second Chair Stand repetition test, single repetition maximal leg and chest press, and grip strength in the affected and nonaffected hand.

Statistical Analysis

Normally distributed continuous variables were compared with mean and SD using independent samples *t*-tests and nonnormally distributed continuous variables were compared with median and interquartile range using Wilcoxon signed-rank sum tests. Categorical variables were assessed using χ^2 test or Fisher exact test.

Time-to-dropout or last study visit differences between the 2 groups were compared using Kaplan-Meier curves to estimate the event-free survival function at 90 days and total study time. Log rank tests were used to assess the differences in time-to-dropout between the 2 groups.

Pre-to-post differences in cognitive functioning, mood, and motor functions within treatment groups were assessed using paired samples *t* tests using the intention-to-treat population. Pre-to-post test differences were calculated for each participant and were used as a dependent variable in multivariable linear regression models adjusted for baseline characteristics to compare group differences.

In addition, we conducted repeated-measures multivariate analyses of covariance for different cognitive domains. Each cognitive domain was made up of tests that have been shown to load on that factor. For example, a multivariate memory domain was constructed by including Hopkins Verbal Learning Test Revised total recall, Hopkins Verbal Learning Test Revised delayed recall, Brief Visuospatial Memory Test-R immediate recall, and Brief Visuospatial Memory Test-R delayed recall. This multivariate approach limits type-1 alpha errors by only examining univariate memory tests if the multivariate composite was statistically significant. These analyses were done by intention-to-treat and per protocol considering only those in the CARET+CTI group with 90% or greater attendance at training sessions. The multivariate analyses of variance provides an *F* test for the Main Effects of Time (independent of the intervention Effect), and the Main Effect Group (independent of the Time Effect). Any treatment effect on the memory composite would be identified by the Intervention × Time interaction, which is testing differential change of the study groups across time.

Safety analyses were conducted per protocol. Chi-square tests or Fisher exact tests were used to assess intervention safety by comparing the frequency of participants with any AEs and the relatedness and seriousness of those AEs between the 2 study groups.

All statistical analyses were conducted using SAS version 9.4 (SAS Inc., Cary, NC).

Study data were collected and managed using REDCap electronic data capture tools.[10]

RESULTS

Adherence and Feasibility

We enrolled 131 participants, of whom 86 were randomized to the CARET+CTI and 45 randomized to the control group. Baseline characteristics are shown in Table 1. There were more women and diabetic patients in the control group. The mean body mass index was higher in the control group. A total of 37 participants withdrew from the study, of whom 17 (20%) were in the CARET+CTI and 20 (44%) were in the control group. In the control group, 42% and in the intervention group, 63% of participants completed at least 80% of scheduled sessions (odds ratio 2.31 CI [1.00–5.34; *P*=0.05]). Figure shows the time and rate of withdrawals during the 12-week intervention phase and the reasons for withdrawals per study group. The observed over expected visit ratio was significantly greater in the intervention than in the control group (0.74±0.30 versus 0.54±0.38; *P*=0.003), confirming better adherence to CARET+CTI (FigureA).

The most common reason for withdrawal was lack of time/having to return to work, newly arising medical issues, and that the control intervention was not challenging enough (FigureB).

Safety

A total of 99 AEs were reported among 59 participants. AEs were reported in 41 (48%) of CARET+CTI participants and in 18 (40%) control group participants (*P*=0.48). The most common AEs were musculoskeletal complaints, including mild back pain, upper or lower extremities pain, or discomfort from exercise (n=26), infections, including urinary tract infection, upper and lower respiratory tract infections, (n=10), and blood pressure abnormalities (n=10). Serious AEs occurred in 8 (20%) participants in the intervention and in 7 (39%) participants of the control group (*P*=0.64). There were no related and serious AEs in either group.

Cognition, Mood, and Quality of Life

The MoCA score significantly improved in the intervention group, but not in the control group (Table 2).

Table 1. Baseline Characteristics of Intervention and Control Groups

	Tot (n=131)		
	Intervention (n=86)	Control (n=45)	*P* Value
Sociodemographics			
Age, y, mean (SD)	59 (11)	58 (12)	0.55
Women, n (%)	26 (30)	24 (53)	0.01
Race, n (%)			
White	51 (59)	20 (44)	0.17
Black	30 (35)	20 (44)	
Other	5 (6)	5 (10)	
Ethnicity, n (%)			
Hispanic	47 (55)	21 (47)	0.38
Non-Hispanic	38 (44)	23 (51)	
Unknown	1 (1)	1 (2)	
Years of education, mean (SD)	13 (4)	13 (3)	0.62
Clinical risk factors			
Hypertension, n (%)	72 (84)	36 (80)	0.37
Dyslipidemia, n (%)	60 (70)	30 (67)	0.92
Diabetes mellitus, n (%)	23 (27)	20 (44)	0.04
Atrial fibrillation, n (%)	4 (5)	3 (7)	0.53
BMI, mean (SD)	29 (4)	31 (5)	0.01
CAD, n (%)	6 (7)	4 (9)	0.68
Stroke characteristics			
Days from stroke to enrollment (median)	154	148	0.60
Ischemic, n (%)	70 (81)	38 (84)	0.47
Ischemic stroke subtype			
Cardioembolism, n (%)	9 (13)	6 (16)	0.11
Large vessel disease, n (%)	30 (43)	9 (24)	
Small vessel disease, n (%)	22 (31)	20 (53)	
Other cause, n (%)	9 (13)	3 (8)	
NIHSS, median (Q1, Q3)	3 (1;4)	2 (1;4)	0.92
mRS, median (Q1, Q3)	2 (2;3)	2 (2;3)	0.71

BMI indicates body mass index; CAD, coronary artery disease; NIHSS, National Institute of Health Stroke Scale; and mRS, modified ranking scale.

After adjusting for baseline differences, and comparing intra-individual changes among the groups, however, no significant differences were noted. Mood improved significantly in both groups during the study and no differences were found after adjustments. We noted significant improvement in quality of life using the Stroke Impact Scale in both arms at the end of the intervention, but no differences were noted between study groups.

Baseline and 3-month neuropsychiatric tests data are shown in Table S2. Cognitive domain–based analysis indicated there was no statistically significant Treatment × Time interaction effects (P=0.57), indicating that treatment and comparison groups did not show different patterns of change from the baseline to the post-test interval. The same results were obtained when differences in baseline demographic variables were examined in multivariate analysis of covariance models.

Physical Assessments

Table 3 shows the changes in strength and cardiovascular fitness during the study. A comparison of averaged intra-individual changes between the groups was not significant after adjusting for baseline differences. Significant improvements were seen in the intervention group across most assessments, and generally non-significant improvements in the control group.

DISCUSSION

We found a supervised combined aerobic, strength, and cognitive training intervention to be feasible and safe after stroke and we were able to demonstrate satisfactory participant adherence. We also noted improvements in cognition, mood, endurance, and strength. However, these did not differ significantly between groups.

Stroke impacts multiple facets of physical and neuropsychiatric functions. The effects on muscle strength are often readily apparent; however, impairments in cardiovascular fitness, cognitive performance, and mood are much less evident. Immediately following stroke, cardiovascular fitness is reduced by almost 50%.[11] Deficits in attention, executive function, and psychomotor speed cause persistent cognitive impairment in almost two thirds of stroke patients. Poststroke anxiety and depression have a prevalence of about 10% and 30%, respectively, and independently affect recovery.[12,13]

Designing a multifaceted intervention, comprising a wide range of physical activity and cognitive stimulation, may be the approach needed to target the multiple effects of stroke. Providing animals with an enriched environment improves sensorimotor function poststroke.[14] Very little of such work has been done in humans. This led us to design the current study and assess the feasibility, safety, and compliance to such a demanding intervention.

Our intervention group had an adherence rate of 80% and three quarters of all scheduled visits were kept over the 3-month interval. Prior studies assessing exercise-based interventions have generally shown high adherence rates, which have varied between 80% and 100%.[15–18] However, drawing such comparisons is difficult because the exercise regimens vary in their intensity and duration. None of the prior studies required the time commitment imposed by our study.

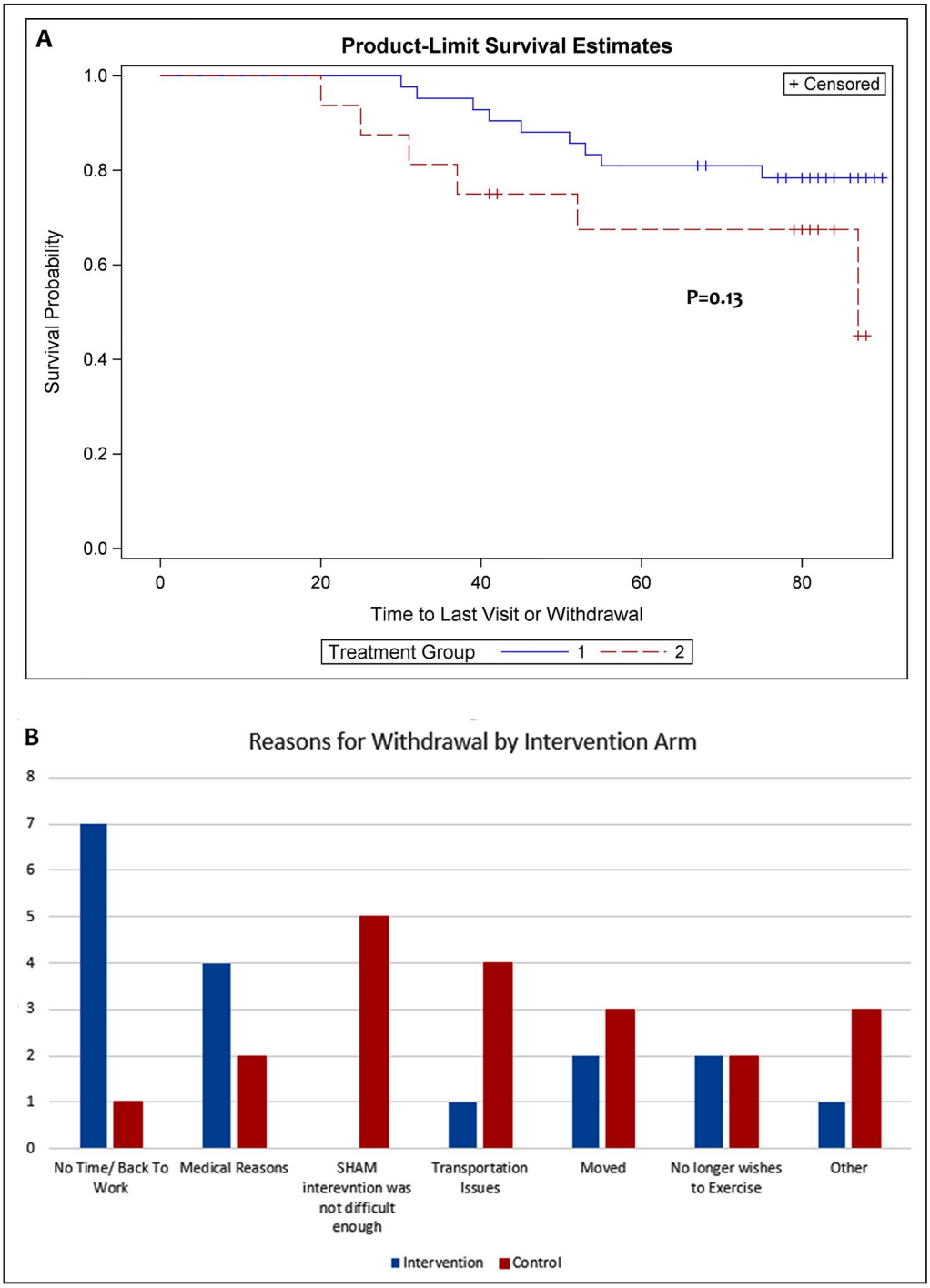

Figure. **A, Kaplan-Meier curves demonstrating earlier and more frequent withdrawals in the control group and (B) reasons for withdrawing.**

Combining physical and cognitive training at each session virtually doubled the time of the intervention. We therefore feel that our adherence rates, which were comparable to prior studies, demonstrate feasibility to conduct a more challenging poststroke intervention.

However, we did find difficulties with adherence in the control group. Their rate of attrition was high and over half of scheduled visits were missed. Having a positive control is necessary for the scientific rigor of the study. The control group was asked to perform simple stretching exercises, which did not keep the participants sufficiently engaged. A frequent complaint and reason for withdrawal was that the sham intervention was not challenging enough (Figure). We were not able to physically separate the 2 groups during their training, and seeing the extra training the intervention

Table 2. Cognitive Assessments, Mood, and Quality of Life

Intervention Arm (Total n=131)	Baseline	3-Month Follow-up	Paired *t* Test *P* Value	Averaged Intraindividual Change	*P* Value*
MoCA score, mean (SD)					
Intervention (n=86)	19.5 (5.6)	20.7 (5.6)	0.02	0.7 (2.5)	0.13
Control (n=45)	20.7 (5.7)	21.1 (6.0)	0.67	0.2 (2.9)	
CES-D score, mean (SD)					
Intervention (n=86)	16 (12)	12 (10)	0.01	−3 (10)	0.70
Control (n=45)	18 (12)	14 (12)	0.01	−5 (10)	
SIS-16, mean (SD)					
Intervention (n=86)	64 (12)	68 (11)	<0.0001	5 (10)	0.77
Control (n=45)	63 (14)	66 (12)	0.01	6 (11)	

CES-D indicates Center for Epidemiological Studies Depression Scale; MoCA, Montreal Cognitive Assessment; and SIS-16, stroke impact scale
*Analyses adjusted for sex, diabetes mellitus, and body mass index.

group was receiving may have been an additional factor contributing to the decision to leave the study.

Adherence was also hampered by the need to return to work and lack of time, as well as medical and transportation issues. The mean age of our study population was relatively young, well within the working age. Strokes were mild, making the return to work more pressing. We were not able to accommodate work schedules by providing after-hours training, nor were we able to provide transportation. Future studies with similar interventions and participant demographics should consider after-hours training sessions and provide transportation, perhaps through ride sharing. Newly arising medical problems were another reason for decreased compliance with scheduled visits. These, however, may be unavoidable given the many medical comorbidities of stroke patients. Even though medical issues arose during the study, we report an excellent safety profile of the intervention. No serious AEs directly related to the intervention were noted. In

Table 3. Physical Assessment Outcomes at Baseline and After 3 Months in the Intervention and Control Groups

Intervention Arm (Total n=131)	Baseline	3-Month Follow-Up	Paired *t* Test *P* Value	Averaged Intraindividual Change	*P* Value*
6-min walk test (m), mean (SD)					
Intervention (n=86)	365 (155)	415 (163)	<0.0001	51 (97)	0.0.64
Control (n=45)	339 (159)	341 (164)	0.14	30 (97)	
Timed Up & Go (s), mean (SD)					
Intervention (n=86)	19 (13)	16 (12)	<0.0001	−4 (6)	0.42
Control (n=45)	23 (26)	17 (13)	0.21	−2 (8)	
15-meter walk speed test (s), mean (SD)					
Intervention	18 (16)	15 (12)	0.004	−3 (11)	0.10
Control (n=45)	18 (14)	35 (83)	0.5	11 (78)	
30-s Stand Chair Test (rep.), mean (SD)					
Intervention (n=86)	9 (5)	11 (5)	<0.0001	2 (4)	0.24
Control (n=45)	9 (5)	9 (4)	0.32	0.5 (3)	
1RM upper body (kg), mean (SD)					
Intervention (n=86)	34 (21)	42 (21)	<0.0001	10 (8)	0.06
Control (n=45)	26 (15)	29 (18)	0.13	4 (10)	
1RM lower body (kg), mean (SD)					
Intervention (n=86)	41 (40)	114 (47)	<0.0001	25 (29)	0.55
Control (n=45)	72 (41)	90 (44)	0.02	15 (28)	
Handgrip affected arm (kg), mean (SD)					
Intervention (n=86)	21 (13)	23 (14)	0.002	3 (7)	0.50
Control (n=45)	18 (11)	18 (9)	0.32	1 (4)	

1RM indicates 1 repetition maximum.
*Analyses adjusted for sex, diabetes mellitus, and body mass index.

addition, we did not find differences in AE between the groups.

Our secondary end point was to investigate the effect of the intervention on cognition. The potential beneficial role of physical activity on cognition is increasingly recognized.[2,19] Recommendations from the National Academy of Medicine to improve cognition have included conducting more studies of combined interventions.[20] In a recent meta-analysis, the combination of resistance and aerobic training poststroke was associated with the most robust cognitive improvement even in the chronic stages of stroke.[2] Our hypothesis was that combining resistance and aerobic with cognitive training after stroke may even have additive benefits on cognitive recovery after stroke. We found only a modest gain in the MoCA score in the intervention group, which did not differ from the control group (mean increase 0.7 versus 2.2 points). The reasons for these findings remain uncertain, and identifying a group of "responders" may be a strategy to target participants most likely to benefit in future studies of similar intervention.

We also want to draw attention to our computerized cognitive training exercises. Only a few studies investigated the impact of structured computerized cognitive training in stroke survivors. In a pilot study, Westerberg et al[21] described significant improvement in working memory in 18 chronic poststroke patients after a 5-week computerized cognitive intervention compared with 18 controls that received no intervention. van de Ven et al. [22] investigated the effect of 58 half-hour computerized cognitive training sessions delivered in a 12-week period, compared with mock cognitive training and no training. Computerized training was well accepted by participants and provides a cost-effective strategy for cognitive training.

Limitations of our study were the difficulties in keeping the control group engaged enough to complete the intervention, which was a reason for the high dropout rate in the sham intervention. We were not able to analyze the proportion of participants who met the preset targets for heart rate and resistance training during each individual training session. However, by providing a 1-to-1 training staff, we were able to ensure that each individual met these goals as much as possible. We feel confident that our participants, who had very low pre-intervention and prestroke exercise levels, were physically challenged by the training. In addition, our intervention period may have been too short to show significant differences between the groups, particularly regarding cognitive outcomes, the results of which may also have been influenced by practice effect. The urban setting of our study population and difficulty with access to transportation may also have limited adherence. We were not able to include a blinded assessment of outcomes. However, every effort was made to have the training and outcome assessment be done by a different study member for a particular participant. Our study was innovative by using a combined cognitive and aerobic plus resistance training. However, we were not able to incorporate all 3 training programs during each session and only 1 session a week was dedicated to aerobic training with 2 sessions for resistance training (cognitive training was performed in every session). Strengths of our study included the large number of participants compared with prior studies that investigated combined interventions. Our study offered a multifaceted intervention, and supervised cognitive and physical training, with a 1-to-1 individual exercise session overseen by trained instructors. We were able to recruit racially/ethnically diverse study participants, and this allowed us to investigate stroke recovery and cognitive and physical outcomes in minority populations.

In conclusion, we report that a combined aerobic, strength, and cognitive training intervention is safe, feasible, and has satisfactory participant adherence over 12 weeks. While we found greater gains in strength, cardiovascular fitness, and cognition in the intervention group when compared with an active control group, these differences were not significantly different after the intervention. We believe that our findings support the conduct of more definitive studies investigating the role of a multifaceted physical activity and cognitive training intervention for stroke recovery.

ARTICLE INFORMATION

Received December 17, 2019; accepted March 27, 2020.

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Acknowledgments

We would like to acknowledge our fellows, our research assistants, and our Bugher Center for Stroke Excellence partners at UCLA, and at UC Denver. We thank Eric Cardenas for his technical assistance in preparation of the figures.

Sources of Funding

This work was supported by the American Heart Association/American Stroke Association/Bugher Foundation.

Disclosures

None.

Supplementary Materials

Data S1
Tables S1 and S2
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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

The exercise training portion of the study was overseen by Dr. Tiozzo, who has a Ph.D. in exercise physiology. All team members involved in the exercise portion of the study went through training sessions with Dr. Tiozzo on proper protocol and training procedures, and had either an exercise physiology background, or were on a pre-med or exercise physiology degree track. Cognitive training was carried out by the coordinator or study team members who had been trained on the protocol and undergone practice sessions with the coordinator prior to administering the cognitive training. Trainers were overseen during the first few sessions to ensure a thorough understanding of proper training procedures. All cognitive assessments were performed by the coordinator who was trained and then approved by Dr. Loewenstein on the administration of the neuropsychological test battery.

Table S1. Cognitive Training.

Computerized training was done through Posit Science (San Francisco, California). Programs were selected based on their ease of use for these age groups, and the adaptability of the programs to each participant's current level of function. Specifically, these computerized programs adjust to the level of difficulty according to the individual's performance by increasing the number of stimuli, decreasing stimulus presentation time or response time, or increasing working memory demands. These programs have a strong track record of use in clinical trials.[5-7] (for additional details please access: https://www.brainhq.com). Specific training components are as follows:

Visual Attention

Target Tracker (Posit Science). The participant must keep track of one or multiple arrays of moving targets with an increasing number of targets added to increase complexity. Speed of the targets and contrast change as different levels of proficiency are met.

Double Decision (Posit Science): This is a modification of the road tour useful field of view (UFOV) Training Program, initially used in the ACTIVE Trial to improve visual processing speed and ability to use visual information in a divided-attention format.[5] Participants have to choose which of two objects (cars) they saw after one appears briefly in the middle of the screen. But at the same time, they have to notice where a Route 66 road sign appears in the periphery of the screen. Speed of the targets change as different levels of proficiency are met.

Processing Speed

Eye for Detail (Posit Sciences). This task requires the participant to make saccades more quickly, and to notice subtle details of targets with each one. Three to five images briefly appear one at a time in different positions on the screen. As the subject becomes more proficient they flash by quicker. Some of the pictures are similar but not the same while others match perfectly.

Fine Tuning (Posit Science)

This task produces two similarly sounding targets at different speeds requiring the participant to discriminate between the targets and to enhance auditory processing speed.[6]

Working Memory

Scene Crasher (Posit Science). Participants are required to train their visual working memory by quickly taking in and remembering the details of a scene. In the exercise, the participant will see several items (such as sheep or keys) flash on screen. After they disappear, they reappear—but with one additional item. The task is to remember the scene from the first flash well enough to spot what changed when it reappears.

Executive Function

Card Shark (Posit Science). Participants are presented with playing cards that are added one at a time to a sequence. Once presented, the card is turned over. Their task is to decide if the current card matches the card presented a specific number of steps back in the sequence.

Juggle Factor (Posit Science). Participants are presented with a sequence of numbers that are placed within moving circles. Their task is to reconstruct the sequence in the right order and in the right locations. The number of items in the sequence grows as they improve at the task. As they progress through training, the moving object trajectories become more complex and the speed increases.

Table S2. Neuropsychological assessments at baseline and 3 months follow up.

Test	**Intervention Arm (tot n =131)**	**Baseline Score**	**3-month follow-up Score**
HVLT total recall, mean (SD)	Intervention (n=86)	19 (6)	22 (6)
	Control (n=45)	19 (6)	22 (8)
HVLT delay recall, mean (SD)	Intervention (n=86)	6 (3)	7 (3)
	Control (n=45)	6 (3)	7 (3)
HVLT recognition/ discrimination index, mean (SD)	Intervention (n=86)	9 (3)	9 (2)
	Control (n=45)	9 (3)	10 (2)
BVMTR total recall, mean (SD)	Intervention (n=86)	16 (9)	20 (8)
	Control (n=45)	18 (10)	21 (10)
BVMTR delay recall, mean (SD)	Intervention (n=86)	6 (4)	7 (3)

	Control (n=45)	6 (4)	8 (4)
BVMTR copy, mean (SD)	Intervention (n=86)	11 (2)	12 (1)
	Control (n=45)	11 (2)	11 (3)
WAIS digit symbol, mean (SD)	Intervention (n=86)	34 (17)	37 (18)
	Control (n=45)	32 (18)	32 (23)
Digit span backwards correct, mean (SD)	Intervention (n=86)	4 (2)	5 (2)
	Control (n=45)	4 (2)	5 (3)
D-KEFS inhibition uncorrected, mean (SD)	Intervention (n=86)	3 (6)	3 (5)
	Control (n=45)	3 (5)	2 (2)
D-KEFS color naming uncorrected, mean (SD)	Intervention (n=86)	1 (3)	0.3 (0.7)
	Control (n=45)	1 (3)	0.2 (0.5)

D-KEFS color naming time to complete, mean (SD)	Intervention (n=86)	49 (18)	44 (18)
	Control (n=45)	47 (16)	44 (15)
D-KEFS inhibition/switching time, mean (SD)	Intervention (n=86)	109 (44)	98 (39)
	Control (n=45)	101 (35)	103 (40)
Cogstate corrected one back, mean (SD)	Intervention (n=86)	25 (9)	26 (9)
	Control (n=45)	25 (9)	25 (9)
Cogstate error one back, mean (SD)	Intervention (n=86)	14 (11)	14 (13)
	Control (n=45)	15 (13)	14 (14)
Cogstate speed one back, mean (SD)	Intervention (n=86)	3 (0.4)	3 (0.1)
	Control (n=45)	3 (0.1)	3 (0.6)
	Intervention (n=86)	23 (10)	26 (9)

Cogstate corrected two back, mean (SD)	Control (n=45)	25 (9)	24 (9)
Cogstate error two back, mean (SD)	Intervention (n=86)	17 (9)	18 (14)
	Control (n=45)	18 (11)	17 (12)
Cogstate speed two back, mean (SD)	Intervention (n=86)	3 (0.4)	3 (0.2)
	Control (n=45)	3 (0.1)	3 (0.1)
Cogstate set shifting corrected, mean (SD)	Intervention (n=86)	112 (22)	115 (19)
	Control (n=45)	111 (25)	107 (28)
Cogstate set shifting error, mean (SD)	Intervention (n=86)	56 (20)	58 (20)
	Control (n=45)	51 (17)	51 (15)
Cogstate set shifting speed, mean (SD)	Intervention (n=86)	3 (0.3)	3 (0.3)
	Control (n=45)	3 (0.2)	3 (0.3)

HVLT - Hopkins Verbal Learning test; BVMTR- Brief Visuospatial Memory Test Revised; DKEFS- Delis-Kaplan Executive Function system, WAIS- Wechsler Adult Intelligence