



A PHYSICAL ACTIVITY INTERVENTION TO PREVENT COGNITIVE DECLINE AFTER STROKE: SECONDARY RESULTS FROM THE LIFE AFTER STROKE STUDY, AN 18-MONTH RANDOMIZED CONTROLLED TRIAL

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Objective: To examine the effects of individualized regular coaching and exercise on post-stroke cognitive and emotional function.

Methods: The Life After Stroke (LAST) study investigated the differences between intervention and care-as-usual between 3 and 21 months post-stroke. Outcome measures were the Trail Making Test (TMT) A and B, Mini Mental State Examination (MMSE), Hospital Anxiety and Depression Scale (HADS), and adherence to the intervention.

Results: Of the 362 patients included in the study, 177 were assigned to the intervention. The mean age was 71.7 years (SD 11.3) and 39.5% were female. The adjusted mean difference between groups for TMT A was 8.54 (95% CI 0.7 to 6.3), $p=0.032$, for TMT B 8.6 (95% CI -16.5 to 33.6), $p=0.50$, for MMSE -0.1 (95% CI -0.8 to 0.6), $p=0.77$, for HADS A -0.2 (95% CI -0.9 to 0.5), $p=0.56$ and for HADS D -0.1 (95% CI -0.7 to 0.5), $p=0.76$. A higher level of adherence to the intervention was significantly associated with increased MMSE ($B=0.030$ (95% CI 0.005–0.055), $p=0.020$).

Conclusion: No clinically relevant effects on cognitive or emotional function were found of individualized regular coaching for physical activity and exercise. However, increased adherence to the intervention was associated with improved cognitive function.

Key words: stroke; intervention; physical activity; cognition.

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Physical activity and exercise is recommended to stroke survivors for prevention of stroke recurrence (1) and to improve functional outcome (2). Best practice recommendations include promotion of physical activity and advice to engage in regular exercise of moderate-to-high intensity levels on most days of the week (1). However, the levels of intensity in post-stroke physical activity are often light-to-moderate (3).

LAY ABSTRACT

Physical activity may help to keep the brain healthier and preserve cognitive ability and mood years after a stroke. In The Life After Stroke (LAST) study, stroke survivors were allocated into 2 groups. A training group was encouraged to perform physical activity for 30 min daily, and 45–60 min of moderate-to-intense physical exercise every week. A control group was followed by their general practitioner as usual. This study aimed to measure the effect on cognitive and emotional function in both groups after 18 months. Of the 362 participants, almost half were in the training group. The mean age was 72 years and 40% were female. There were no differences between the groups regarding effect on cognitive or emotional function. In conclusion, this study did not show an effect of the physical training programme on cognition or mood after stroke.

Interventions based on risk assessment and risk factor management post-stroke are increasingly common, with stroke recurrence or physical function as outcome (4, 5). Prevention of cognitive decline in high-risk persons is shown to be possible when physical, cognitive, vascular and nutritional interventions are given regularly (6). A recently published meta-analysis of randomized controlled trials (RCTs) showed a positive effect of physical activity on cognitive performance post-stroke (7), especially on attention and processing speed and through programmes combining aerobic interventions and stretching. However, the included studies involved young patients, small sample sizes, and interventions lasting from 4 to 24 weeks. So far, multifactorial interventions aiming to prevent post-stroke cognitive decline have not been shown to be effective, possibly due to heterogeneity, short follow-ups, and low intensity (8).

The Life After Stroke (LAST) study assessed the effect on motor function of individualized regular coaching on physical activity and exercise for 18 months post-stroke (9). Despite neutral results on primary outcome, the aim of the current study was to investigate whether the intervention could improve cognitive or

emotional function in stroke survivors. In addition, this study explored the association between adherence to the intervention and the outcome variables.

METHODS

LAST is a prospective, randomized, single-blinded, multicentre, 2-arm parallel group clinical trial. Between October 2011 and January 2016, patients were recruited 3 months post-stroke from 2 Norwegian hospitals; Trondheim University Hospital and Bærum Hospital with intervention and follow-up for 18 months in the primary healthcare services in the municipalities of Trondheim, Asker and Bærum (NCT01467206) (10). The current study analysed secondary outcomes.

Participants

Inclusion criteria were: patients aged over 18 years, with first-ever or recurrent stroke due to infarction and intracerebral haemorrhage, community-dwelling with modified Rankin Scale (mRS) score <5 . Exclusion criteria were serious medical comorbidity with short life-expectancy, cognitive deficits, as evaluated by Mini Mental State Examination (MMSE) <21 points (or <17 points for patients with aphasia) and contraindication to participate in motor training (10). Neurological impairment was measured by the National Institute of Health Stroke Scale (NIHSS), which ranges from zero to 42. The patients were treated in the acute and subacute phase according to international and national guidelines from 2011 (11). Risk assessment and individualized secondary prevention was initiated at discharge from hospital after the index stroke, with recommendation for long-term risk factor control as part of usual care.

Randomization

Participants were stratified according to functional level post-stroke (mRS >2 points), age ≥ 80 years and recruitment site, and randomized by a web-based randomization system developed and administered by the Unit of Applied Clinical Research, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway. Patients randomized to the control group received usual care.

Intervention

In addition to usual care, the intervention group received regular individualized coaching performed by physiotherapists, aiming to achieve physical activity 30 min daily, and 45–60 min physical exercise including 2–3 bouts of vigorous activity every week. The intervention did not include supervised or observed training. The physiotherapists carried out home visits to provide education and tailored training programmes, based on the patient's preferences and goals. The patients were encouraged to report their activities in standardized training diaries. The patients had a monthly meeting with their coach, going through training diaries, with reassessment according to needs. These meetings were face-to-face in the first 6 months. For the next 6 months, every second meeting could take place as a phone meeting. During the final 6 months, 4 of the 6 meetings could take place as a phone meeting.

Outcomes

Cognitive function was measured using standardized neuropsychological tests assessing for global function, processing speed

and executive function (normal scores); MMSE (minimum score 0 to maximum score 30), Trail Making A and B (TMT A (<60 s considered a normal score) and B (<180 s considered a normal score) (12, 13) at inclusion 3 months post-stroke and at 18 months follow-up. Symptoms of anxiety and depression were assessed by Hospital Anxiety and Depression Scale (HADS A and D) (14). Each domain consists of 7 questions with scores ranging from 0 (no symptoms) to 3 points. The outcomes were changes in cognitive and emotional measures from baseline to 18 months follow-up.

Adherence to the intervention was measured using self-reported activity through the diaries and evaluation by the physiotherapists, defined as the number of weeks patients in the intervention group completed at least 210 min of physical activity (minimum 30 min every day) and 45 min of exercise (in total per week). Despite considerable variation, it has been shown that the participants established and maintained moderate-to-good adherence to the intervention (15).

Statistical analyses

Sample size was calculated according to the primary outcome (Motor Assessment Scale) in the main study (9). Descriptive statistics are given as mean (SD), median (interquartile range), or frequency (percentage), where relevant. According to the CONSORT instructions, all outcomes underwent intention-to-treat (ITT) analysis (16). Linear regression analyses were used, with TMT A and B, MMSE and HADS A and D, respectively, as dependent variables, and intervention group, age, sex, stroke severity (measured by mRS), hospital site, treatment group, and cognitive or emotional status at inclusion as covariates.

For patients in the treatment arm, linear regression analyses were carried out with the cognitive and emotional outcome measures, TMT A, TMT B, MMSE, HADS A, and HADS D, at 18-month follow-up from baseline, as dependent variables, one at a time, with adherence to physical activity and exercise as primary covariate. These regression analyses were carried out both unadjusted and adjusted for the following covariates, one at a time and simultaneously: age, sex, mRS, MMSE, if appropriate, and the corresponding outcome variable score, all measured at baseline 3 months post-stroke.

On HADS and MMSE, the subjects with less than 50% missing values on a scale, the missing values were imputed singly using the expectation-maximization algorithm on that scale. Thereafter, multiple imputation was used to impute missing scale sums and other missing values, with $m=100$ imputation, as recommended by van Buuren (17). Patients who died during follow-up were excluded from the analyses. The normality of residuals was checked by visual inspection of QQ plots. Two-sided p -values <0.05 were considered statistically significant, and 95% confidence intervals (95% CI) are reported where relevant.

Ethics

The study was approved by the Regional Committee of Medical and Health Research Ethics (REK no 2011/1427) and registered with ClinicalTrials.gov, number NCT01467206. All participants provided informed consent.

RESULTS

In total, 380 patients were recruited and randomized in the main study (the trial profile is reported elsewhere;

Table I. Baseline characteristics ($n = 362$)

| Assessment | Intervention ($n = 177$) | Control ($n = 185$) |
|---|----------------------------|-----------------------|
| Demographics | | |
| Female, n (%) | 78 (44.1) | 65 (35.1) |
| Age, years, mean (SD) | 71.4 (11.3) | 72.0 (11.3) |
| Stroke subtype, n (%) | | |
| Cerebral infarction | 163 (92.1) | 166 (89.7) |
| Cerebral haemorrhage | 14 (7.9) | 19 (10.3) |
| Risk factors, n (%) | | |
| Hypertension | 85 (48.0) | 104 (56.2) |
| Previous stroke/TIA | 26 (14.7)/20 (11.3) | 35 (18.9)/16 (8.6) |
| Diabetes | 24 (13.6) | 27 (14.6) |
| Coronary heart disease | 18 (10.2) | 24 (13.0) |
| Atrial fibrillation | 28 (15.8) | 41 (22.2) |
| Lung disease | 18 (10.2) | 23 (12.4) |
| Assessments | | |
| NIHSS, mean (SD) | 1.47 (2.2) | 1.70 (2.5) |
| NIHSS <8, n (%) | 172 (97.2) | 179 (96.8) |
| NIHSS 8–16, n (%) | 5 (2.8) | 6 (3.2) |
| NIHSS >16, n (%) | 0 (0) | 0 (0) |
| mRS, mean (SD) | 1.44 (1.1) | 1.44 (1.1) |
| mRS 0–2, n (%) | 141 (79.7) | 146 (78.9) |
| mRS 3–4, n (%) | 36 (20.3) | 39 (21.1) |

Coronary heart disease: previous myocardial infarction or present angina pectoris and heart failure; atrial fibrillation: permanent or paroxysmal atrial fibrillation; NIHSS: National Institute of Health Stroke Scale; IQR: interquartile range; mRS: modified Rankin Scale; TIA: transient ischaemic attack; SD: standard deviation.

186 patient were randomised to intervention and 194 to standard care (9). After exclusion of 18 patients who died during follow-up (9 from the control group and 9 from the intervention group), 362 patients were included in these ITT analyses; 185 were assigned to control and 177 to intervention. Mean age was 71.7 years (SD 11.3), 39.5% were female and 329 (90.9%) had had ischaemic stroke. The baseline characteristics are shown in Table I.

Measures of cognitive function and emotional symptoms showed a slight decline in both groups during follow-up (Table II). The adjusted mean difference between groups for TMT A was 8.54 (95% CI 0.7 to 16.3), $p = 0.032$, for TMT B 8.6 (95% CI –16.5 to 33.6), $p = 0.50$, for MMSE –0.1 (95% CI –0.8 to 0.6), $p = 0.77$, for HADS A –0.2 (95% CI –0.9 to 0.5), $p = 0.456$ and for HADS D –0.1 (95% CI –0.7 to 0.5), $p = 0.76$. The results based on multiple imputations are presented

in Table II. The results from complete case analyses showed the same trends (data not shown).

Unadjusted regression analysis applied to the intervention arm showed a significant association between increasing adherence to the intervention and improvement on TMT A, TMT B and MMSE. However, only MMSE remained significant in the adjusted analysis ($B = 0.030$ (95% CI 0.005–0.055, $p = 0.020$) (Table III).

DISCUSSION

This study investigated the effectiveness of an individualized physical activity and exercise intervention programme on cognitive and emotional function post-stroke compared with usual care. The intervention involved regular coaching to perform 30 min physical activity daily every day and 45–60 min of physical exercise with 2–3 bouts of vigorous intensity levels every week. No clinically relevant effect of this programme was found on cognitive or emotional functioning after 18 months compared with usual care. However, regression analysis applied to the treatment arm only showed a positive association between increasing adherence to the intervention and cognitive function.

To our knowledge, this is the first RCT to investigate the effect of a long-term physical activity programme on cognitive and emotional function post-stroke in a rather large cohort with high mean age. The lack of clinical impact on cognitive measures is in line with the neutral results shown by the primary and secondary functional measures (9). There was no effect on emotional function, which is in contrast to a recent study published by Graven et al. (18), who also included life-management, barriers and social network. However, our explorative analysis showed an association between good adherence to the intervention and better cognitive function, in line with the findings from the meta-analysis (7).

Since motor recovery after stroke tends to reach a plateau phase after 10 weeks (19), the initial improve-

Table II. Results of the intervention. Analyses based on multiple imputation of missing values

| Outcome | Intervention group ($n = 177$) | | Control group ($n = 185$) | | Between-group differences, change from baseline to 18 months* | |
|---------|----------------------------------|-----------------------------|-----------------------------|-----------------------------|---|------------|
| | Baseline Mean (SE) [n] | 18 months Mean (SE) [n] | Baseline Mean (SE) [n] | 18 months Mean (SE) [n] | Estimate (95% CI) | p -value |
| TMT A | 60.5 (2.9) [156] | 70.1 (4.2) [133] | 64.4 (2.6) [169] | 66.0 (3.3) [139] | 8.54 (0.74 to 16.3) | 0.032 |
| TMT B | 149.4 (7.4) [132] | 155.8 (9.7) [108] | 169.8 (7.9) [142] | 161.3 (12.0) [101] | 8.6 (–16.5 to 33.6) | 0.50 |
| MMSE | 27.9 (0.2) [176] | 27.5 (0.3) [143] | 28.0 (0.2) [182] | 27.5 (0.3) [156] | –0.1 (–0.8 to 0.6) | 0.77 |
| HADS A | 3.6 (0.3) [177] | 3.6 (0.3) [149] | 3.7 (0.3) [180] | 3.8 (0.3) [157] | –0.2 (–0.9 to 0.5) | 0.56 |
| HADS D | 2.9 (0.2) [177] | 3.7 (0.2) [149] | 3.5 (0.2) [180] | 3.9 (0.3) [157] | –0.1 (–0.7 to 0.5) | 0.76 |

*Regression coefficient for treatment group in regression analysis, adjusted for age, sex, stroke severity (modified Rankin scale at inclusion), hospital site and the baseline measure of the relevant variable (TMT A, TMT B, MMS, HADS A or HADS B).

SE: standard error; CI: confidence interval; MMSE: Mini Mental State Examination; TMT A: Trail Making Test A; TMT B: Trail Making Test B; HADS: Hospital Anxiety and Depression Scale; HADS A: HADS Anxiety; HADS D: HADS Depression.

Table III. Linear regression with the different outcome variables as dependent variables and adherence to physical activity and exercise as primary covariate, unadjusted and adjusted for additional covariates

| | TMT A (n = 177) | | TMT B (n = 177) | | MMSE (n = 177) | | HADS A (n = 177) | | HADS D (n = 177) | | | | | | |
|---|-----------------|------------------|-----------------|--------|------------------|---------|------------------|----------------|------------------|-------|-----------------|-------|--------|------------------|-------|
| | B | CI | p-value | B | CI | p-value | B | CI | p-value | B | CI | | | | |
| Unadjusted | | | | | | | | | | | | | | | |
| Adherence to physical activity and exercise | -0.463 | -0.803 to -0.123 | 0.008 | -0.843 | -1.551 to -0.135 | 0.020 | 0.038 | 0.012 to 0.064 | 0.004 | 0.010 | -0.015 to 0.034 | 0.444 | -0.019 | -0.042 to 0.004 | 0.109 |
| Adjusted separately for | | | | | | | | | | | | | | | |
| Age | -0.310 | -0.621 to 0.000 | 0.050 | -0.569 | -1.220 to 0.083 | 0.087 | 0.030 | 0.005 to 0.055 | 0.018 | 0.010 | -0.015 to 0.034 | 0.950 | -0.001 | -0.021 to 0.019 | 0.926 |
| Sex | -0.464 | -0.804 to -0.124 | 0.008 | -0.848 | -1.556 to -0.140 | 0.019 | 0.038 | 0.012 to 0.064 | 0.004 | 0.009 | -0.015 to 0.034 | 0.454 | -0.007 | -0.028 to 0.014 | 0.498 |
| mRS at baseline | -0.383 | -0.705 to -0.062 | 0.019 | -0.731 | -1.420 to -0.041 | 0.038 | 0.036 | 0.011 to 0.062 | 0.005 | 0.011 | -0.013 to 0.036 | 0.367 | -0.005 | -0.026 to 0.016 | 0.632 |
| MMSE at baseline | -0.475 | -0.819 to 0.131 | 0.007 | -0.812 | -1.536 to -0.089 | 0.028 | NA | NA | NA | 0.009 | -0.015 to 0.034 | 0.455 | -0.007 | -0.028 to 0.014 | 0.509 |
| Outcome variable score at baseline | -0.047 | -0.307 to 0.213 | 0.723 | -0.195 | -0.777 to 0.387 | 0.510 | 0.039 | 0.014 to 0.065 | 0.003 | 0.011 | -0.010 to 0.033 | 0.301 | -0.002 | -0.019 to 0.015 | 0.831 |
| Adjusted for all | -0.035 | -0.288 to 0.217 | 0.785 | -0.112 | -0.694 to 0.470 | 0.705 | 0.030 | 0.005 to 0.055 | 0.020 | 0.011 | -0.011 to 0.034 | 0.316 | 0.004 | -0.013 to -0.021 | 0.651 |

Analysis based on multiple imputation of missing values and patients randomized to the intervention group.

TMT A: Trail Making Test A; TMT B: Trail Making Test B; MMSE: Mini Mental State Examination; HADS A: The anxiety domains of Hospital Anxiety and Depression Scale; B: regression coefficient; CI: confidence interval.

ment in cognitive function may follow a similar pattern (20), suggesting that earlier initiation, and perhaps more specific and intensive, future interventions would be beneficial. In addition, the intervention was based on patient's preferences more than the type of training aiming at cognitive gain. Combining aerobic exercise with other training programmes seems to achieve better cognitive function and might be applied in future trials (7, 21).

The lack of effect on cognition might be explained by lack of adherence to the intervention. However, another possible explanation for no effect on cognition is the heterogeneity of the stroke population and, probably also, the underlying brain pathology (22). Theoretically, the effect of physical activity on brain function includes neurogenesis, building brain reserve, angiogenesis and prevention of progressive small vessel disease (23). Light-to-moderate physical activity may represent a treatment strategy less likely to affect the underlying pathology in the chronic phase. However, it might halt or slow decline through building brain reserve and thereby delay symptom onset. A potential benefit on vascular pathology, to prevent cognitive dysfunction due to chronic cerebral hypoperfusion may need longer follow-up. Physical activity could have a beneficial effect on cognitive flexibility and brain reserve, but an effect through neurogenesis and angiogenesis may be achieved through interventions with higher intensities (22). Secondary prevention after cerebrovascular disease involves both pharmacological treatment and interventions for behaviourally modifiable risk factors (24). A multimodal individualized intervention including optimal medication, dietary, social and cognitive stimulation in addition to physical activity might also be needed to improve cognition after stroke, perhaps with longer follow-up (25–27).

Post-stroke, there is also a wide spectrum of neuropsychological manifestations. Apparent brain damage gives rise to different cognitive deficits, especially executive function, attention and processing speed and working memory (28, 29). It is a limitation that HADS, MMSE and the Trail Making Tests are primarily designed as screening tools and might not be sensitive to detect changes that occur during follow-up after stroke. Hence, future research should investigate the psychometric properties of these measures in the stroke population. Furthermore, the study population may, due to the rather high mean age, have been too heterogeneous regarding both underlying additional degeneration and comorbidities. In addition, the study was designed or powered for a potential effect on functional outcome, and length of education was not registered. Furthermore, functional impairments in the dominant arm/hand may have affected the results

on the cognitive test performance. The intervention was individualized coaching on physical activity and exercise, and did not include supervised exercise. Therefore, the actual performed training is self-reported regarding both length and intensity. Finally, only mild-to-moderate strokes were included, pre-stroke disability and comorbidities were not assessed, and the generalizability of the results may be affected by the fact that our sample may have been more motivated to undertake physical activity and exercise regardless of the result of the randomization.

In conclusion, this study found no effect of the intervention on cognitive function post-stroke compared with usual care. However, increased adherence to physical activity and exercise was associated with improved cognitive function, indicating that the intervention dose might be of importance to achieve a benefit. Future preventive trials should include education regarding healthy lifestyle and focus on motivation to adhere to the physical programme over time. In addition, participants should be stratified into subgroups based on supposed reversibility, especially those with small-vessel disease or pure vascular pathology, in order to prevent further decline.

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