Aerobic Training Efficacy in Inflammation, Neurotrophins, and Function in Chronic Stroke Persons: A Randomized Controlled Trial Protocol

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Background: Neuroinflammation is an important part of stroke pathophysiology and has both detrimental and beneficial effects after stroke. Besides that the enhancement of neurotrophins seems to be related to improvements in stroke recovery. Evidences suggest that exercise plays a role in modulating anti-inflammatory and neurotrophic effects. However, little is known about its impact in stroke survivors, mainly in chronic stroke. The purpose of this study is to investigate the efficacy of moderate-intensity treadmill exercise in changing inflammatory mediators, interleukin-6 (IL-6), soluble tumor necrosis factor receptors I and II (sTNFRI, sTNFRII), interleukin-10 (IL-10), and brain-derived neurotrophic factor (BDNF) levels in chronic stroke patients. The secondary objective is to investigate the effects of training in improve mobility and exercise capacity. *Methods*: This is a randomized controlled trial. Chronic stroke patients will be randomized to an experimental or control group, and will receive group interventions three times per week, over 12 weeks. The experimental group will receive moderate-intensity (60%-80% of maximum heart rate reserve) treadmill exercise. Control group will perform walking training on the ground (<40% of maximum heart rate reserve). Primary outcomes include IL-6, sTNFRI, sTNFRII, IL-10, and BDNF levels. Secondary outcomes include mobility and exercise capacity. Outcomes will be measured at baseline, postintervention, and at the 4-week follow-up. *Discussion*: The findings of this trial have the potential to provide important insights regarding the effects of an aerobic physical program in the inflammatory process and in the neuronal plasticity in stroke persons and its impact on mobility and exercise capacity.

Key Words: Aerobic exercise—inflammation—BDNF—stroke

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Introduction

Stroke is an important cause of disabilities worldwide and two thirds of deaths caused by stroke occur in low and middle-income countries, like Brazil.[1,2] Stroke is caused by the interruption of the blood supply to the brain, because a blood vessel bursts (hemorragic stroke) or is blocked by a clot (ischemic stroke). This cuts off the supply of oxygen and nutrients, causing damage to the brain tissue.[3] Ischemic stroke represents more than 80% of all cases and results in the decrease of adenosine triphosphate with concomitant ionic imbalance, neurotransmitter release, and inhibition of its reuptake.[4] It is followed by an initial excitotoxicity and inflammation over days, resulting in apoptotic cell death of nearby tissue in the penumbra area. Inflammation is an important part of stroke pathophysiology and has both detrimental and beneficial effects. Recruitment of immune cells, expression of inflammatory mediators, and blood-brain barrier disruption is responsible for neuronal loss. However, activation of the microglia, astrocytes, and endothelial cells also can be neuroprotective and promote brain regeneration and recovery.[4-7]

TNF, a cytokine typically involved in the acute phase of the systemic inflammation, is significantly elevated in both ischemic and hemorrhagic stroke patients compared to control ones[5] and it suggests that TNF is related to the size and severity of lesion.[6] The measurement of soluble TNF receptors (sTNFR1 and sTNFR2) is more stable and reflects with great accuracy the state of activation of the TNF/TNF receptor system.[8] IL-6 is a multi-functional cytokine involved in a wide range of biological activities like generation of the acute phase reactions, regulation of the immune system and it is associated with the metabolism during exercise.[9] IL-6 is a T cell and macrophage derive cytokine and it is considered a robust pro-inflammatory biomarker in the context of stroke but, paradoxically, IL-6 plays a beneficial role when liberated after muscle contractions.[5-6,10-13] So, it is considered a classical adipomyokine, exerting its roles depending on the production site.[12] IL-10 is a potent anti-inflammatory mediator, and, if overexpressed, can suppress neuronal degeneration.[14] It works on stroke, neutralizing TNF and interferon gamma (IFNγ) inflammatory effects. It appears to be produced by the leukocytes in response to exposure to muscle derived IL-6.[5,15]

Brain-derived neurotrophic factor (BDNF) is a neurotrophin which is involved in stroke inflammatory and immunologic response, as part of the recovery of it.[5] It has been shown to promote motor function recovery and it is involved in relearning motor skills. However, animal model studies suggest a limited time period to increase cerebral plasticity after stroke,[16] and most of studies in humans assess BDNF concentration in acute stroke.[17,18]

There has been an extensive research over the past decades about the pathophysiology of stroke during the first few weeks in both animal models and human studies. However, there has been very little research on chronic stroke, defined as a period of 6 or more months after stroke onset. Many studies focused on the process of acute inflammation and intended to define biological markers for early stroke.[5,12,19,20]

Chronic stroke is an important area of research because it can be associated with long-term disabilities. Mobility difficulties were cited as a self-reported problem by 58% of stroke survivors.[21] Cardiorespiratory fitness is diminished and VO2 peak among stroke persons is about 50% of age- and gender-matched healthy persons.[22,23] There is a decrease in muscle mass, strength, and power, which, associated with inactivity, leads to atrophy both in the paretic and nonparetic limbs, resulting in reduced physical function and functionality.[2]

In spite of the relevance and prevalence of chronic stroke disabilities, there are few studies addressing this phase. Histological assessment of autopsied human brains showed the presence of inflammatory cells (eg, macrophages) in chronic stroke.[24] Immune factors, vascular adhesion molecule-1, and thrombin-anti thrombin complex, were elevated in African-Americans at least 6 weeks poststroke compared to control individuals.[25] Noonam et al[26] evidenced the presence of a sustained peripheral inflammatory response (measured by levels of C-reactive protein − CRP − and white cell count) at 18 months post-stroke in an elderly stroke sample of 149 individuals, when compared to matched age controls. The maintenance of an inflammatory state was verified also in another study, in which the levels of adiponectin and CRP performed 1 year after stroke, showed no statistical differences from the acute level ones, measured within 24 hours after the insult. Adiponectin (ADPN) is a recently discovered adipocytokine, whose low plasma concentrations have been associated with greater risk of chronic degenerative diseases. It is suggested that this adipocytokine has insulin-sensitizing, antiatherogenic, and antiinflammatory properties.[27]

Neuroimune and neurotrophic responses can be modulated by physical activity including in patients with neurological diseases, besides influencing whole body and brain health.[2,19,28-33] Processes such as apoptosis, excitotoxicity, and inflammation can be reduced by physical activity. The expression of neurotrophic factors such as BDNF can also be upregulated by it, mainly by aerobic exercise.[19,29,31,32] However, few existing studies investigated the effect of exercise programs in inflammation or plasticity in individuals with stroke, and even more in its chronic phase. There has been found only one protocol study aiming to investigate the impact of aerobic exercise on stroke subacute persons.[20] Another study investigated the impact of aerobic exercise program in BDNF levels in subacute and chronic ischemic stroke subjects, focusing on cognitive functions in patients with lesions in the territory of anterior circulation.[31]

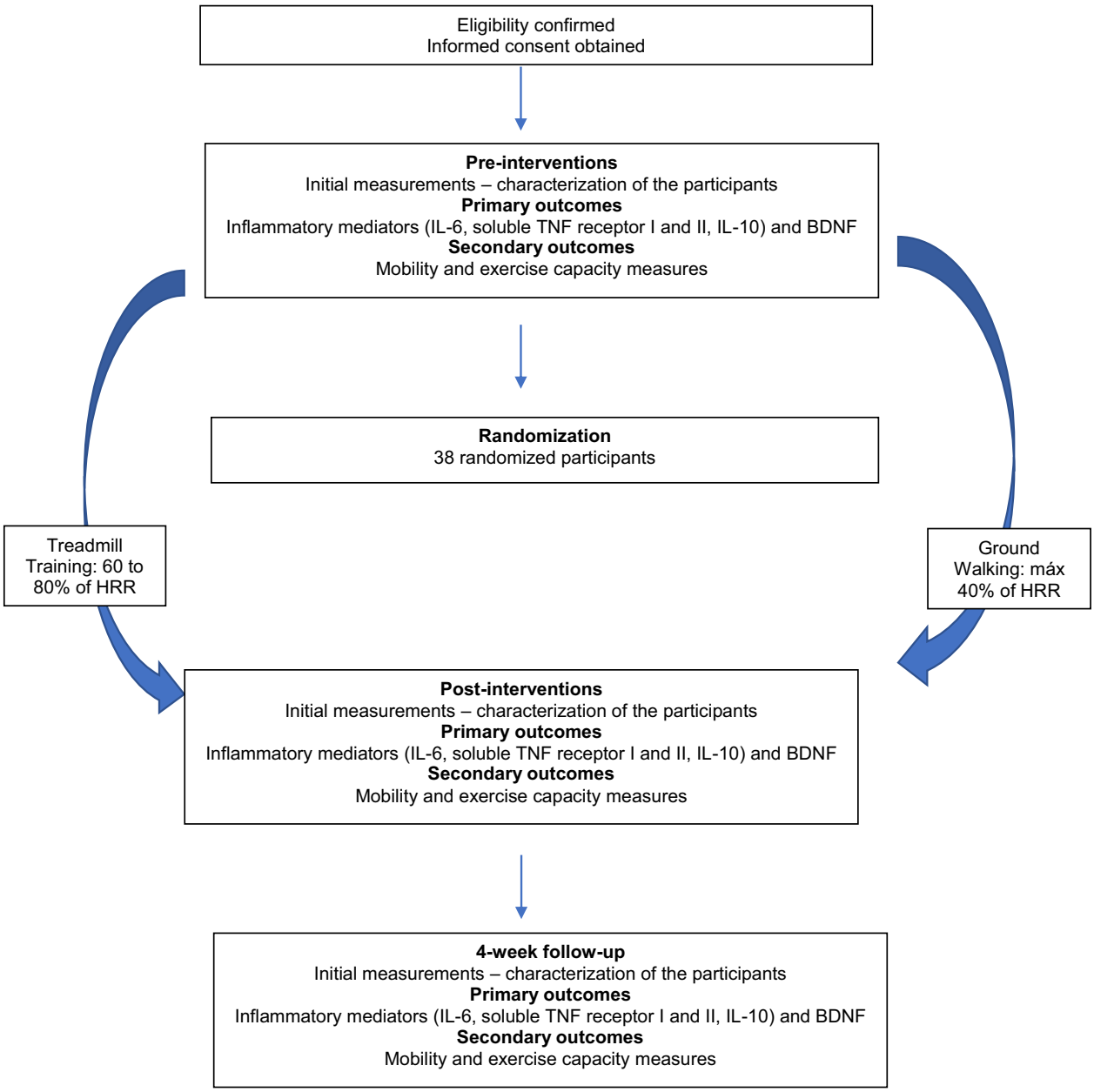

Figure 1. *Flow diagram of the planned trial pathway for the effects of aerobic exercise post stroke.*

Therefore, the purpose of this study is to investigate the efficacy of moderate-intensity treadmill exercise in improving inflammatory mediators (IL-6, sTNFR1 and sTNFR2, IL-10) and BDNF levels in individuals with chronic stroke using a double-blinded, randomized controlled clinical trial. The secondary objective is to investigate the effects of training in improving mobility and exercise capacity in chronic poststroke individuals.

Methods/Design

Study Design

A prospective randomized controlled trial with concealed randomization, blinded assessors, and intention-to-treat analysis will be carried out with individuals who have suffered a stroke (Fig 1). Participants will be randomly allocated to the experimental or control group. Both groups will undertake training sessions of 40 minutes, three times a week over 12 weeks. The interventions will be carried out in groups of three or four participants. Blood samples and outcome measures will be collected by trained researchers at baseline, postintervention, and 4-week follow-up. Data collection and analysis will be performed by a research blinded to the group allocation.

All the participants will be informed about the tests and the use of the results and will need to give informed consent. This study was approved by the Institutional Research Ethical Committee (CAAE: 79105217.1.0000.5149)

of the Universidade Federal de Minas Gerais, Belo Horizonte, Brazil. The trial was registered at the Brazilian Clinical Trials Registry (U1111-1207-0819).

Patient Population: Inclusion and Exclusion Criteria

The participants will be recruited from different settings (ie, academic and community). The criteria inclusion will be (1) clinical diagnosis of first or recurrent chronic stroke (>6 months), (2) ≥18 years of age, (3) patient should be inactive or insufficiently active according to the *Centers for Disease Control and Prevention*,[34] (4) adjusted activity score (AAS) at the Human Activity Profile under 74 (classified as impaired or moderately active),[35,36] and (5) medical permission for physical activity.

The exclusion criteria will be (1) cognitive impairments according to the Mini-Mental State Exam cut-off scores,[37] (2) language impairments (comprehensive aphasia), (3) pain and/or other adverse health conditions that may interfere with the performance of the intervention, and (5) patients on medication or who have inflammatory and autoimmune diseases that may interfere with inflammatory and neurotrophin levels will also be excluded.

Randomization

The randomization sequence will be computer-generated in blocks of two using sequentially numbered opaque closed envelopes. A research assistant, who will not be involved in the study, will prepare the envelopes prior to the study. After the recording baselines measures, participants will be randomly allocated to either the experimental or control group by the intervention therapist who will reveal the contents of the sealed opaque envelopes.

Interventions

Participants in both groups will undergo 40-minute training sessions, 3 days per week, for 12 weeks (36 sessions). Before the session, patients should be at rest for ten to fifteen minutes for blood pressure, heart rate, and oxygen saturation measurements. Trained researchers will conduct the sessions in groups with three or four participants.

The participants of the experimental group will receive moderate-intensity treadmill exercise. Patients will be submitted to 5 minutes warm-up walking at comfortable speed on the treadmill. Then, they should maintain for 30 minutes at 60%-80% of the maximum heart rate reserve (HRR), which will be determined according to the cardiopulmonary exercise test (CPET).[38-40] If it is not possible to begin with this intensity, the intensity will be defined by the subjective perception of the effort and the heart rate. The progression of the training will be determined by the trained researcher, adjusted for the individual capacity and the slope of the treadmill will remain at 0°. Heart rate and oxygen saturation will be monitored all the time. Finally, participants will walk for 5 minutes at comfortable speed on the treadmill for cooling (Table 1).

The participants of the control group will receive ground walking training. Patients will be submitted to 5 minutes at comfortable speed for warm-up. Then, they should walk for 30 minutes keeping their heart rate less than 40% of the reserve heart rate. Heart rate and oxygen saturation will be monitored all the time. Finally, they will walk for 5 minutes at comfortable speed for cooling (Table 2).

Procedures

Procedures demographic, anthropometric, and clinical information will be obtained, followed by collection of the primary and secondary outcomes.

Outcomes Measures

Primary Outcomes

Primary outcomes to be are inflammatory mediators (IL-6, sTNFR1 and sTNFR2, IL-10) and BDNF levels. Blood will be drawn by aseptically venipuncture in vacuum tubes. In order to rule out any confounding factors caused by circadian rhythm, all samples will be collected at the same time of the day. After procedures, blood will be stored at −70°C until assayed by enzyme-linked immunosorbent assay (ELISA). Inflammatory mediators and BDNF levels will be measured using commercially available ELISA kits (DuoSet, R&D systems, Minneapolis, MN) and reported as pg/mL. These procedures and analysis will be performed at Neurobiology Laboratory from Morphology Department from the Instituto de Ciências Biológicas da Universidade Federal de Minas Gerais, Brazil.

Table 1. *Experimental group intervention training*

Activity	Time	Procedures
Participants arrival Rest, on a sited and comfortable position	10 min	AP, HR, and SpO_2 measures
Warming	5 min	Walking on treadmill at comfortable speed
Aerobic training	30 min	Walking on treadmill at 60% to 80% of the maximum heart rate reserve (HRR) FC monitoring during all the time. PA and SEP monitored at each 10 min
Refreshing	5 min	Walking on treadmill at comfortable speed

Table 2. *Control group intervention training*

Activity	Time	Procedures
Participants arrival Rest, on a sited and comfortable position	10 min	AP, HR, and SpO_2 measures
Warming	5 min	Walking on ground at comfortable speed
Training	30 min	Walking on ground at less than 40% of the maximum heart rate reserve (HRR) FC monitoring during all the time. PA and SEP monitored at each 10 min
Refreshing	5 min	Walking on treadmill at comfortable speed

Secondary Outcomes

Secondary outcomes to be are mobility and exercise capacity. Mobility will be measured by the tests maximal and comfortable gait speeds and the Timed '"Up and Go" (TUG) test. These tests are very applied and recommended to assess mobility in subjects with stroke. They provide adequate measures of subjects' mobility, are easy to administer, and do not require any specialized training or equipment.[41]

For assessing gait speed, subjects will have to walk at both their maximal and most comfortable speeds along a 14 m hallway, wearing their normal shoes. Patients can be tested wearing orthotics or using preferred walking devices. The time to cover the central 10 m is recorded with a digital stopwatch and the speed (m/s) calculated. It is a reliable measure for gait speed in stroke persons.[42,43] For the TUG test, subjects must be sat comfortably on a chair with height adjusted to 100% of their leg length and will be instructed to walk at their self-selected comfortable speed for 3 m, turn around, return, and sit down again. The time, in seconds, will be recorded. TUG demonstrated to be consistent in measuring mobility in stroke persons after 3 months of stroke[44] and in subjects with chronic stroke.[45] For both tests, a familiarization trial will be performed, and after a 1-minute rest, they will perform three trials of each test, and the average of it will be recorded.

Exercise capacity will be evaluated by the 6-minute walk test (6MWT). The 6MWT was originally developed to assess people with cardiovascular and respiratory disease, but nowadays it is commonly used as a measure of walking endurance and is a significant predictor of community ambulation and integration in stroke survivors.[46] The test will be applied on a flat surface, following the recommendations of the American Thoracic Society, for a distance of 25 m and the maximal distance the participant can walk, as fast as possible, during 6 minutes will be recorded.[46,47]

Data Monitoring

Database management and statistical analyses will be performed by an independent blinded to the group allocation researcher. The treating therapists will monitor the doses and compliance with training.

Sample Size

The sample size was calculated according to the differences in BDNF average values before and after intervention obtained in the El-Tamawy's study.[31] Based on these values, with 80% power, at a two-tailed significance level of 0.05, 16 patients per group will be required (a total of 32 patients). Assuming a dropout of 15%, a total of 38 participants will be recruited (19 per group).

Statistical Analyses

Descriptive statistics will be used to summarize baseline data. Category variables will be compared between groups by use chi square test. Between-group comparisons of baseline quantitative characteristics will be performed with Mann-Whitney *U*-test or independent Student's *t*-test. Analysis of covariance will be used to eliminate the influence of extraneous factors when there is a difference between the groups at baseline.

The effects of the interventions will be analyzed from the data collected and by intention-to-treat analyses. There are two factors (group × time), with repeated measures on the time factor. Two-way analyses of variance with repeated measures at all time-points for primary and secondary outcomes will be used to evaluate the differences between groups. Group descriptions will be presented as mean (SD) and effect sizes with 95% confidence intervals (CIs) will be reported.

Data analyses will be performed using Statistical Package for the Social Sciences (SPSS) for Windows (release 17.0; SPSS, Chicago, IL, USA).

Discussion

Stroke is an important cause of morbidity and most of individuals with stroke have mobility limitations, difficulties in daily activities and participation.[48,49] They already present reduced cardiorespiratory fitness, which may reduce their levels of physical activity.[22,23] Neuroinflammation underlies all this process and plays a central role at both pathogenesis and functional recovery after it.

Aerobic exercise has been demonstrated to be a beneficial tool in improving physical fitness and functional recovery and in reducing inflammation in many groups

of individuals, but there are not enough evidences about this intervention in stroke persons, mainly in Brazilian persons with stroke. Moreover, most of the few existing studies investigated the effect of exercise programs in inflammation or plasticity in individuals with acute or subacute stroke.[20,31]

Given the high prevalence and level of incapacity of stroke around the world and the known existence of an inflammation level in persons with chronic stroke, the aim of this study is to investigate the impact of an aerobic moderate intensity exercise program in inflammatory mediators and BDNF levels in individuals with chronic stroke.

If this kind of exercise is shown to be effective for stroke persons in this study, it should be used by physical therapists to improve function in persons with stroke, since it is an available choice for being used at rehabilitation programs. The findings of this study probably can provide important insights about the effectiveness of aerobic training in improving mobility, functional recovery, and changing of inflammatory mediators and BDNF levels on stroke. Patients, physical therapists, and public health systems may be helped from it, and it can generate future positive economic and social impacts.

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