Available online at www.sciencedirect.com
ScienceDirect
Contemporary Clinical Trials 29 (2008) 410–417
Contemporary Clinical Trials
www.elsevier.com/locate/conclintrial

The ExStroke Pilot Trial: Rationale, design, and baseline data of a randomized multicenter trial comparing physical training versus usual care after an ischemic stroke

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Received 25 May 2007; accepted 25 September 2007

Abstract

Introduction: A high level of physical activity is associated with a decreased risk of first stroke and physical activity modifies recognized stroke risk factors and is recommended for stroke survivors. Available research shows that stroke patients can increase their level of physical performance over a short period. When the intervention period is over, physical performance often declines towards baseline level. Currently, there is no evidence on the association between physical activity and the risk of recurrent stroke. The ExStroke Pilot Trial is a randomized clinical trial with the aim of increasing stroke patients' level of physical activity and secondarily to associate the level of physical activity to the risk of recurrent stroke, myocardial infarction, and all-cause mortality in the two groups. We describe the rationale, design, and baseline data of the ExStroke Pilot Trial.
Methods: Patients with ischemic stroke above 39 years were randomized to intervention or control group. The intervention group will, over a 2-year period, receive information on and verbal instruction to exercise by a physiotherapist or a physician. The control group will receive the department's usual care. Physical activity is assessed in both groups seven times during follow-up using the Physical Activity Scale for the Elderly (PASE) questionnaire, which quantifies the amount of physical activity done in the last seven days prior to interview. The PASE score constitutes the primary outcome measure. The secondary outcome is the time from randomization to recurrent stroke, myocardial infarction, or all-cause mortality. Further outcome measures include: time from randomization to recurrent stroke, myocardial infarction, and vascular death; recurrent stroke; modified Rankin Scale; quality of life; occurrence of falls and fractures.

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1551-7144/$ - see front matter
doi:10.1016/j.cct.2007.09.008

Trial status: From 9 centers in 4 countries, 314 patients were included and follow-up is ongoing. Mean age and standard deviation (SD) of the study participants was 68.4 (11.9) years and 56.4% were male. Mean (SD) PASE score was 84.1 (55.9) and median (interquartile range) Scandinavian Stroke Scale score was 54 (51–58).

Keywords: Ischemic stroke; Physical activity; Secondary prevention; Randomized clinical trial

1. Introduction

The importance of physical activity as a stroke risk factor has been investigated in a number of observational studies [1–6]. A meta-analysis showed that level of physical activity is inversely associated with the risk of stroke [7]. Small randomized trials have shown that training can improve stroke patients' ability to walk [8], maintain balance [9], and do daily chores [10]. Non-randomized studies show that physical exercise can improve hemiparetic stroke patients' peak oxygen uptake and gait performance [11,12]. Exercise based cardiac rehabilitation has been shown to reduce mortality in patients with coronary heart disease [13]. So far no clinical trials have been designed to show if physical activity can reduce mortality and the risk of recurrent stroke in stroke survivors. The main characteristic of trials of physical activity in stroke is that the intervention period is short. The level of physical fitness can be increased during the intervention period, but is usually not maintained after the end of the trial intervention. The ExStroke Pilot Trial is designed to assess how repeated encouragement and verbal instruction affect stroke patients' level of physical activity over a 2-year period.

2. Method

2.1. Study design

The ExStroke Pilot Trial is an ongoing randomized, multicenter, multinational trial with blinded outcome assessment. Patients were centrally randomized to intervention group or control group. The intervention consists of repeated encouragement and verbal instruction on being physically active given by a physiotherapist or a physician. The control group receives usual care, including information on the possible benefits of physical activity. Five centers in Estonia, Poland, China, and Denmark participate in the trial.

2.2. Inclusion criteria

Within 90 days of symptom onset patients with an ischemic stroke over 39 years of age were considered for inclusion. All patients had a computed tomography (CT) or magnetic resonance imaging (MRI) scan compatible with ischemic stroke before inclusion. Patients needed to be able to walk unassisted by another person. Canes and walkers were allowed. All patients had to give informed consent, verbal and written, prior to enrollment.

2.3. Exclusion criteria

Patients who were bedridden, in wheelchair, unable to understand the trial, reluctant to provide informed consent, or had CT/MRI scans suggesting intracerebral hemorrhage or other focal pathology not indicating ischemic stroke were excluded from the trial.

2.4. Scandinavian Stroke Scale

Stroke severity was assessed using the Scandinavian Stroke Scale (SSS) [14]. The SSS is a simple stroke scale and consists of the following 9 items: consciousness, orientation, eye movement, facial palsy, arm motor power, hand motor power, leg motor power, gait, and speech. The SSS score may range from 0–58 where full score means no deficits in these items.

2.5. Randomization

Centralized randomization 1:1 was performed by telephone or e-mail within gender, age (40–70 years or >70 years), and stroke severity (Scandinavian Stroke Scale 20–39 points or 40–58 points) strata in blocks of 10. Stratified randomization was chosen in order to keep the two groups balanced with regard to gender, age, and stroke severity, as we presumed that these factors would influence the PASE score the most.

2.6. Experimental intervention

Patients randomized to the intervention group were scheduled for a meeting with a physiotherapist or a physician soon after randomization. The patients and the physiotherapist or the physician then planned a detailed training program. The training program was individualized taking into account the patients' resources and prior training status as well as the patients' preferences for leisure time physical activities and the feasibility of activities in the local community. A guideline was developed for the physiotherapist/physician to use when planning the training program for the individual patients. Specifically, the symptoms of the patients should be taking into considerations so patients with more severe pareses were instructed differently from patients without pareses. Furthermore the guideline instructed the physiotherapist/physician to contact their patient once in between clinical visits to discuss the training program, training progress, and how the patient complied with the training program. Each patient met with their personal physiotherapist/physician every three months the first year and thereafter every six months until the end of the trial.

2.7. Control intervention

Patients randomized to the control group received treatment as usual without any specific information about physical activity, but were told about the possible benefits of physical exercise and that physical activity is recommended for stroke survivors. Patients in the control group were seen for clinical visits at the same time intervals as the patients in the intervention group, but did not see a physiotherapist and were not contacted by telephone in between clinical visits.

2.8. Co-interventions

Both groups were given the same treatment with regard to hypertension, antiplatelet therapy, hypercholesterolaemia, hyperhomocysteinaemia, and diabetes as well as information on smoking, alcohol, and diet.

2.9. The Physical Activity Scale for the Elderly (PASE)

The PASE questionnaire was developed to assess physical activity in the elderly population using age-neutral questionnaires [15,16]. The PASE is a 12-item scale that measures the average number of hours per day spent on leisure, household, and occupational physical activities over the previous seven days. Each item has an activity weight which is multiplied by the amount of time spent on the item. All items are then added to give the PASE score.

The PASE scoring algorithm was derived from physical activity measured by movement counts from an electronic physical activity monitor, activity diaries, self-assessed activity levels in a general population of non-institutionalized persons [15,16]. The activities included (weight): walk outside home (20); light sport (21); moderate sport (23); strenuous sport (23); muscle strength (30); light housework (25); heavy housework or chores (25); home repairs (30); lawn work or yard care (36); outdoor gardening (20); caring for another person (35); work for pay or as a volunteer (21). The PASE score may range from zero to more than 400. When tested in the general population it ranged from 0–361.

The validity of the PASE questionnaire was tested by Washburn et al. [15]. PASE was positively correlated to grip strength ($r=0.37$, $p<0.01$), static balance ($r=0.33$, $p<0.01$), and leg strength ($r=0.25$, $p<0.01$) and negatively correlated to resting heart rate ($r=-0.13$, $p<0.05$), age ($r=-0.34$, $p<0.01$), perceived health status ($r=-0.34$, $p<0.01$), and overall Sickness Impact Profile score ($r=-0.42$, $p<0.01$). PASE was found to vary with changing seasonal temperatures and was highest during the summer. Furthermore, PASE has been correlated to the doubly labeled water method [17], performance on a six-min walk and knee strength in a population with knee pain [18], peak

oxygen uptake, systolic blood pressure and balance [16], average three-day portable accelerometer readings [19] and mean seven-day accelerometer counts/min [20].

PASE has been validated in different populations: Healthy with no cardiac risk factors [17,19], patients with knee pain and cardiac risk factors [18], and sedentary people [16,20]. The mean PASE score ranged from 85 to 131 in six validation studies and the mean age ranged from 67 to 76 years [15–20].

The PASE questionnaire was originally translated by the developers into Chinese (Mandarin) and Danish. In Poland and Estonia the participating investigators translated the PASE questionnaire from English into their native languages.

2.10. Baseline visit

After informed consent patients who fulfilled all inclusion criteria and none of the exclusion criteria were randomized to the intervention group or the control group. A thorough medical history was taken at inclusion focusing on risk factors for stroke and diseases that would compromise physical activities. The focus was on the following risk factors: History of stroke, MI, diabetes mellitus, atrial fibrillation, intermittent claudication, hypertension, hypercholesterolaemia, smoking, and alcohol consumption. Hypertension was defined as a systolic/diastolic blood pressure above 140/90 mmHg at baseline or previously diagnosed by another physician. Hypercholesterolaemia was defined as total cholesterol above 5.0 mmol (195 mg/dl) at baseline or diagnosed by another physician. Alcohol consumption was categorized into 3 groups: Never drinking, moderate drinking (less than 14 units of alcohol per week for women and less than 21 units of alcohol per week for men), and heavy drinking (above moderate levels). Smoking was categorized into the following groups: Never, former, and current smoker. The PASE score obtained at baseline referred to the week preceding the stroke.

2.11. Follow-up

All patients are followed for a maximum of two years. Patients are seen for a clinical visit every three months the first year and thereafter every six months until the end of the trial. At each visit, vital signs, clinical outcome measures, adverse events, concomitant medication, and PASE-score data are collected. To monitor the influence physical exercise may have on quality of life patients are asked to complete the World Health Organizations' Well Being Scale-5 [21] and the European Quality of Life Visual Analogue Scale [22] at each visit. In addition to clinical visits patients in the intervention group will at each clinical visit meet with their personal physiotherapist or physician to discuss their training program and training progression.

2.12. Outcome measures

The primary outcome is the level of physical activity measured with the PASE questionnaire. The secondary outcome is the time from randomization to recurrent stroke, MI, or all-cause mortality. Further outcomes include: time from randomization to recurrent stroke, MI, and vascular death; recurrent stroke; disability measured with modified Rankin Scale [23,24]; quality of life; and falls and fractures. Investigators blinded to randomization will interview all patients about their PASE score and new events.

2.13. Adjudication committee

The outcome event adjudication committee will blindly and independently evaluate and adjudicate all events such as death, causes of death, recurrent stroke, MI and traumatic event or other adverse events.

2.14. Statistics

The difference in PASE score between the two groups will be tested using SAS mixed model for repeated measures. Furthermore differences in PASE score will be tested by calculating the area under the curve for all PASE measurements in the intervention period. The secondary outcomes will be analyzed on an intention-to-treat basis by Cox regression analysis after testing for proportionality, allowing for potential risk factors (baseline variables and covariates). Time to any event will be calculated from the day of randomization. The effect of selected baseline

Table 1
Baseline characteristics of ischemic stroke patients in the ExStroke Pilot Trial

Total number of included patients	314
Age — years	
Mean (SD)	68.4 (11.9)
Range	40 –93
Male — no. (%)	177 (56.4)
Race or ethnic group	
Caucasian	273 (86.9)
Asian	41 (13.1)
Time from stroke to inclusion — days	
Median (IQR)	10 (5–24)
PASE score — Mean (SD)	84.1 (55.9)
Scandinavian Stroke Scale — Median (IQR)	54 (51–58)
Stroke characteristics, TOAST criteria	
Large-artery atherosclerosis — no. (%)	69 (22.0)
Cardioembolism — no. (%)	40 (12.7)
Small-artery disease — no. (%)	102 (32.5)
Stroke of other determined etiology — no. (%)	2 (0.1)
Stroke of undetermined etiology — no. (%)	101 (32.2)
Selected clinical characteristics	
History of stroke — no. (%)	49 (15.6)
History of transient ischemic attack — no. (%)	29 (9.2)
History of atrial fibrillation — no. (%)	41 (13.1)
History of myocardial infarction — no. (%)	26 (8.3)
Diabetes — no. (%)	45 (14.3)
History of intermittent claudication — no. (%)	26 (8.3)
History of hypertension — no. (%)	171 (54.5)
History of coronary-artery bypass grafting — no. (%)	5 (1.6)
History of percutaneous transluminal coronary angioplasty — no. (%)	5 (1.6)
Hypercholesterolaemia — no. (%) [a]	179 (57.0)
Baseline Modified Rankin score [b] — no. (%)	
0	230 (73.2)
1	48 (15.3)
2	31 (9.9)
3	5 (1.6)
Smoking — no. (%)	
Current smoker	115 (36.6)
Former smoker	108 (34.4)
Never smoked	91 (29.0)
Alcohol — no. (%)	
Never drinking	78 (24.8)
<14/21(f/m) [c]	197 (62.7)
>14/21(f/m)	38 (12.1)

SD: standard deviation. IQR: interquartile range. TOAST: classification of subtype of acute ischemic stroke according to Trial of Org 10172 in Acute Stroke [25].

[a] Hypercholesterolaemia defined as total cholesterol > 5.0 mmol/l (195 mg/dl).

[b] Before stroke onset. Patients with mRS of 4 and 5 were excluded.

[c] Number of drinks on a weekly basis according to gender (f/m).

variables and covariates will be assessed by either stepwise or backward regression methods. Two-sided statistical test will be used and p-value < 0.05 will be considered significant.

2.15. Independent Data Monitoring and Safety Committee

An Independent Data Monitoring and Safety Committee (IDMSC) will monitor all vascular events, falls, and adverse events. The IDMSC will be blinded to randomization. The Copenhagen Trial Unit will provide all data to the IDMSC. The IDMSC can recommend that the trial should stop early if there is a significant ($p < 0.001$) difference in the secondary outcome between intervention and control group. The IDMSC was scheduled to meet twice during the study.

2.16. Data management

All investigators have to maintain a protocol of included patients and case report forms are to be kept in accordance with Good Clinical Practice (GCP). All case report forms will be handled by the Copenhagen Trial Unit, which will enter data into a database for analyses. All data are double entered to diminish the risk of errors. Two instructional visits per clinical site were scheduled to educate investigators in using the PASE questionnaire, to monitor data, and to instruct physiotherapist and physicians on physical exercise.

2.17. Ethical considerations

It is presumed that physical activity will have favorable effect on the prognosis. All patients included in the ExStroke Pilot Trial were therefore informed of the potential beneficial effects of physical activity. The study was approved by the Danish Ethics Committee (KF 11006/04), the Danish Data Protection Agency, and by the local Ethics Committees in China, Poland, and Estonia. The ExStroke Pilot Trial is registered at www.clinicaltrials.gov (NCT00132483).

2.18. Sample size

The sample size was calculated based on a mean difference of 20 PASE points, a standard deviation of 50, an alpha of 5%, and a beta of 20%. Based on a sample size calculation 99 patients would be needed in each group. A total of 300 patients were planned to be included in the ExStroke Pilot Trial to take into account that dropouts could occur.

2.19. Funding

This project is funded by the Ludvig and Sara Elass Foundation, Hede Nielsen Foundation, Eva and Henry Frænkels Foundation, Søren and Helene Hempels Foundation, and King Christian the 10th Foundation. The funding sources have had no impact on the design of the trial and will have no impact on the data collection, data management, data analysis, and reporting.

2.20. Trial status

Screening and patient enrollment started in August 2003 and was completed in October 2005. A total of 314 patients fulfilled entry criteria and were randomized. Patients were included from the following centers: Estonia ($n=9$), Poland ($n=19$), China ($n=41$), Aarhus, Denmark ($n=8$), Hvidovre, Denmark ($n=31$), Frederiksberg, Denmark ($n=15$), Amager, Denmark ($n=40$), Rigshospitalet, Denmark ($n=2$), and Bispebjerg, Denmark ($n=149$). Baseline characteristics for all patients are shown in Table 1. Patients were randomized at a median of 10 days after their stroke, had a mean PASE score of 84, and presented a variety of stroke subtypes defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) groups [25]. More than half of the patients had hypertension and hypercholesterolaemia and about 15% had previous stroke, atrial fibrillation, and diabetes.

3. Discussion

The potential benefits of physical activity have long been recognized and physical exercise is recommended for stroke survivors [26]. Despite the acceptance of physical activity as a beneficial therapy for stroke survivors there is a lack of randomized trials documenting that stroke patients can maintain a long-term increase in physical activity and benefit clinically from it. The ExStroke Pilot Trial will be the first randomized trial designed to show if stroke patients through verbal instruction and encouragement can increase their level of physical activity over a 2-year period.

The ExStroke Pilot Trial is designed as a multicenter trial, in order to facilitate the leap from pilot trial to a large-scale trial. Should the ExStroke pilot trial show a significant increase in PASE score in the intervention group, it would be sensible to conduct a larger trial with recurrent stroke, AMI, and all-cause mortality as the primary outcome measure. This can be done using the same set-up as the ExStroke pilot trial.

The PASE questionnaire was chosen as the instrument for assessing physical activity because it was designed for elderly people. Activities in which elderly people participates are different from those of younger people. Using age-

neutral questionnaire might result in a false low activity score and the sensitivity of an age-neutral questionnaire might not be high enough to register improvements achieved by elderly people.

Our trial has a number of strengths. First, it is multicenter and multinational. This increases its external validity. Second, we conducted centralized randomization in order to minimize allocation bias [27–29]. Third, we employed stratified randomization in order to secure equal distribution of important prognostic factors [30]. Fourth, a trained person blinded to randomization assessed the PASE score to avoid possible assessment bias [27–29]. Fifth, we planned the intervention period to two years, which gives the opportunity to assess how physical activity affects the long-term prognosis after stroke. The intervention period in other trials of physical activity in stroke patients has often lasted from 3 to 6 months. Sixth, the ExStroke Pilot Trial intervention is low cost relative to interventions where regular training sessions are being conducted. This means that if a significant increase in PASE score can be demonstrated, it will be possible to use this method in medical practice if a clinical effect can also be demonstrated.

Our trial also has limitations. First, the ExStroke Pilot Trial is not powered to show any beneficial effect of physical activity on the risk of recurrent stroke, MI, or mortality. Secondly, the PASE questionnaire is validated from age 55 and above. In the ExStroke Pilot Trial we have included patients from the age of 40 years. As PASE is validated in sedentary people and in people with disabilities the PASE questionnaire is assumed sufficiently sensitive to differentiate between the small changes in physical activity, which can be expected in stroke patients.

Third, the ExStroke patients are a selected stroke population. As seen from Table 1 the median baseline SSS score is high, matching a stroke population with mild stroke. In the center that included the majority of patients in ExStroke, all patients with ischemic stroke were assessed over a 3-month period. Only 12 (15%) out of 80 patients were included in the trial. The percentage is likely to have been lower in the other centers. Accordingly, many patients had exclusion criteria or declined to participate, when they were informed about the need of performing physical exercise.

The results of the trial will eventually be applicable to patients with mild ischemic stroke.

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