RESEARCH

ExStroke Pilot Trial of the effect of repeated instructions to improve physical activity after ischaemic stroke: a multinational randomised controlled clinical trial

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ABSTRACT

Objectives To investigate if repeated verbal instructions about physical activity to patients with ischaemic stroke could increase long term physical activity.
Design Multicentre, multinational, randomised clinical trial with masked outcome assessment.
Setting Stroke units in Denmark, China, Poland, and Estonia.
Participants 314 patients with ischaemic stroke aged ≥40 years who were able to walk—157 (mean age 69.7 years) randomised to the intervention, 157 (mean age 69.4 years) in the control group.
Interventions Patients randomised to the intervention were instructed in a detailed training programme before discharge and at five follow-up visits during 24 months. Control patients had follow-up visits with the same frequency but without instructions in physical activity.
Main outcome measures Physical activity assessed with the Physical Activity Scale for the Elderly (PASE) at each visit. Secondary outcomes were clinical events.
Results The estimated mean PASE scores were 69.1 in the intervention group and 64.0 in the control group (difference 5.0 (95% confidence interval −5.8 to 15.9), P=0.36). The intervention had no significant effect on mortality, recurrent stroke, myocardial infarction, or falls and fractures.
Conclusion Repeated encouragement and verbal instruction in being physically active did not lead to a significant increase in physical activity measured by the PASE score. More intensive strategies seem to be needed to promote physical activity after ischaemic stroke.
Trial registration Clinical Trials NCT00132483

WHAT IS ALREADY KNOWN ON THIS TOPIC

Observational studies have suggested that physical activity reduces risk of first stroke
In stroke patients there is little evidence on the effect of physical activity on risk of recurrent stroke or other cardiovascular events
Several small trials have shown that supervised group training can result in improved fitness and walking ability in stroke patients over periods of 3 to 6 months

WHAT THIS STUDY ADDS

This trial of counselling and repeated encouragement to increase physical activity to patients after mild stroke over a period of 24 months did not result in improvement in physical activity

INTRODUCTION

Physical exercise is often recommended for stroke survivors because it is assumed that physical activity may favourably influence the prognosis through its effect on blood pressure, glucose metabolism, and cholesterol level.[1] However, reviews of interventions to promote physical activity found the evidence insufficient to assess its effectiveness.[2 3] Some small randomised trials have shown that supervised physical training can improve stroke patients' balance, walking ability, and physical fitness over periods of three to six months.[4-8]

The ExStroke Pilot Trial was designed to assess if repeated encouragement and verbal instructions regarding how to exercise could result in a sustained increase in stroke patients' physical activity. The rationale and design of the ExStroke Pilot Trial have been described previously.[9]

METHODS

Trial participants

Patients with ischaemic stroke aged ≥40 years from six stroke units in Denmark and from one neurological department each in Chengdu, China, Warsaw, Poland, and Tartu, Estonia, were eligible if they were able to walk unassisted. Canes and walkers were allowed. Between August 2003 and October 2005, participants were enrolled within 90 days of onset of stroke symptoms after giving informed consent. Exclusion criteria were inability to understand the meaning of the trial, unwillingness to participate, medical contraindications to exercise, or a modified Rankin scale (for activities of daily living) of 4 or 5 before the qualifying event (indicating moderately severe to severe disability).[10 11] Stroke severity was assessed at baseline with the Scandinavian stroke scale (SSS).[12]

Interventions

The experimental intervention consisted of repeated encouragement and verbal instruction on being

physically active given by a physiotherapist (or a neurologist in the Chinese centre). The control group received information on the possible benefits of physical activity but no specific instruction. Both groups received standard treatment with antithrombotic drugs, antihypertensive treatment, and statins as needed after individual assessment. Physiotherapists and physicians examined patients during their hospital stay, and rehabilitation was carried out according to the customs of the department.

Patients randomised to the intervention group met up with a trial instructor for development of a detailed training programme to start after discharge from the hospital. Considerable effort was taken to motivate the participants, and the programme was individualised according to each patient's resources, former activities, and preferences. At each visit the instructor and participant would fill in a standard agreement form with various choices of physical activity with a copy of the completed form for the participant to take home. At the follow-up visits—every three months during the first year, and thereafter every six months until the end of the trial—the instructor repeated instructions and adjusted the physical activity plan. Between visits a telephone call was made to remind each participant in the intervention group about the physical activity agreement.

No telephone calls were made in the control group. Participants in the control group received standard treatment without detailed information on physical activity. They were seen for clinical visits with the same frequency as the intervention group.

Assessment of physical activity

At their entry to the study, we ascertained participants' level of physical activity during the week before their stroke, and at each follow-up visit we ascertained their level of physical activity in the week preceding the visit. We used the validated physical activity scale for the elderly (PASE).[13 14] This has 12 questions about different activities (covering walking outside the home, sport, exercises for strength and endurance, housework, home repairs, garden and yard work, caring for another person, and work), and each question has subsidiary questions as to the frequency per week and the time per day spent on the activity. Higher scores indicate a higher level of physical activity.

Outcome measures

The primary outcome was the difference in PASE score between the two groups. Secondary outcomes included the time from randomisation to recurrent stroke, myocardial infarction, or death (from any cause). Other outcomes were time to vascular death, frequency of recurrent stroke, modified Rankin scale, and falls and fractures. See bmj.com for details.

Sample size

To detect an increase in physical activity of 20 PASE points (which we considered a realistic goal, such as walking outside the home for two hours three times a week), we calculated that 99 patients would be needed in each group and planned to recruit a total of 300 patients to allow for dropouts.[9]

Randomisation, masking, and blinding

See bmj.com for details. In each study centre an interviewer masked to the randomisation of the patient obtained the PASE score at the follow-up visits. These interviewers were otherwise uninvolved in the conduct of the trial. They were instructed in how to use the PASE questionnaire and were told not to ask the patients about the group assignment. These investigators also obtained information about recurrent stroke, myocardial infarction, and falls.

Statistical methods

The data were analysed on the basis of intention to treat and of per protocol. A mixed model analysis (proc mixed SAS 9.1) including the repeated measures option was used to assess the time course of PASE (see bmj.com for details). The difference in modified Rankin scale between the two groups at 3, 6, 12, and 24 months after randomisation was assessed with a non-parametric test (Mann-Whitney). Cox analyses were used to assess the effect of the intervention on time to a clinical event.

RESULTS

A total of 314 patients fulfilled the entry criteria, agreed to participate, and were randomised between August 2003 and October 2005. At entry to the study, the two patient groups were similar in terms of sex, age, and stroke severity (a median of 54 points on the Scandinavian stroke scale in both groups, corresponding to mild stroke). Pre-stroke PASE scores tended to be higher in the intervention group (median 76 (interquartile range 50-124)) than in the control group (65 (50-106)). Distribution of atrial fibrillation, diabetes, mean systolic arterial blood pressure, blood glucose, hypercholesterolaemia, pre-stroke modified Rankin scale, and habits of smoking and alcohol consumption were similar in the two groups (see bmj.com).

The table shows the number of participants at each follow-up visit. For participants who were unable to visit the clinic at 24 months, a telephone interview was made. In the intervention group, 80 participants had all six of the planned intervention sessions, 22 had five intervention sessions, 19 had four, 11 had three, 12 had two, nine had one, and four had none. During the study, 11 patients died and three withdrew in the intervention group, compared with nine deaths and two withdrawals among the controls (see bmj.com for details).

Primary outcome measure

The mean PASE scores in the intervention group versus the control group were 69.1 *v* 64.0, respectively (difference 5.0 (95% confidence interval −5.8 to 15.9), P = 0.36). In the intention to treat analysis, the change in score over time was not significantly different between the groups, although the intervention group at 6 and 9 months' follow-up showed a non-significant increase in

Participants' median scores on the physical activity scale for the elderly (PASE) and number attending the follow-up visits in the intention to treat analysis of the ExStroke Pilot Trial

	Intervention group		Control group	
Visit	Median (IQR)	No (%)	Median (IQR)	No (%)
Before stroke	76 (50-124)	156 (99)	65 (50-126)	157 (100)
Follow-up visit:				
3 month	73 (42-120)	126 (80)	68 (43-94)	133 (84)
6 month	86 (50-133)	123 (80)	67 (33-102)	128 (83)
9 month	83 (41-120)	118 (77)	64 (41-104)	124 (80)
12 month	80 (45-130)	118 (77)	69 (36-111)	123 (80)
18 month	76 (46-123)	113 (74)	66 (33-111)	114 (74)
24 month	69 (33-118)	133 (91)	68 (32-106)	143 (97)

IQR = interquartile range; % = percentage of survivors.

PASE score (see table). The control group maintained the pre-stroke PASE score throughout the trial. The small difference between groups in PASE score that was apparent during the week preceding the stroke was maintained during most of the trial period but vanished at 24 months. There was no significant effect of centre and no significant interactions between protocol specified variables and the intervention indicator. The per protocol analysis of the patients who attended all planned follow-up visits (80 patients in the intervention group and 81 patients in the control group) showed a significant (P=0.03) difference in pre-stroke PASE score. Overall, there was no significant difference between the two groups regarding PASE score when adjusted for pre-stroke PASE score.

Of the points that constituted the PASE score, 15% originated from walking outside the home, 46% from household activities, and 13% from yard work. Sports activities accounted for only 10%, caring for another person for 7%, and work for 8%. There were no significant differences between the groups in the distribution of activities.

Other outcome measures

Recurrent stroke occurred in 14 participants in the intervention group and 11 in the control group. Participants were readmitted for these events, of which seven were fatal. There were no significant differences regarding the time to recurrent stroke, myocardial infarction, or all cause mortality. There was no significant difference in disability score (modified Rankin scale) between the two groups at any time point, but disability did increase compared with before stroke. The number of first falls was 53 in the intervention group and 54 in the control group. Several participants fell more than once, the total number of falls were 93 in the intervention group and 94 in the control group. Falls resulting in fractures were not significantly different in the two groups. The recurrent strokes and fractures contributed to the worsening of modified Rankin scale over time.

DISCUSSION

Interpretation of results

The main finding of our trial was that repeated encouragement and verbal instruction did not result in a measurable increase in physical activity. The intervention did not have any significant effect on recurrent vascular events, nor on activity of daily living as measured by the modified Rankin scale.

Stroke survivors might be expected to be motivated to improve their level of physical activity. However, that was not apparent in this trial. More than half of the participants' PASE scores derived from household activities, whereas walking outside the home and sports activities accounted for only a quarter.

Strengths and limitations of study

The strengths of our trial are that it is a multicentre, multinational, randomised clinical trial with masked outcome assessors. The patients had mild strokes and had the physical capability to increase their physical activity. The mixed model analysis is optimal in the presence of missing data since all observations are used to improve the precision, and the mixed model analysis will not be biased even if missing PASE scores depend on observed quantities, such as the choice of intervention used.[15]

It was a weakness that we did not test during the trial whether the participants actually increased their physical activity as measured by the PASE score. The repeated questioning about physical activity in the control group may have contributed to a higher PASE score in this group by reminding participants about the importance of physical activity, which would have reduced our chances of finding an intervention effect. We cannot exclude the possibility that some of the PASE assessors became aware of some of the participants' assigned intervention, but this is unlikely to have affected our results.

Generalisability

The results of the ExStroke Pilot Trial are probably generalisable to patients with mild ischaemic stroke. Although most of the included participants were Danes, there was no indication that patients from the other countries responded differently. A possible selection bias existed since some patients declined to participate because they were not interested in physical training.

General interpretation

Our comparatively low cost intervention of repeated verbal encouragement to be physically active failed to have the desired effect. Supervised group training of long duration might be an alternative avenue to be explored but would be more costly. However, it is still not known if increased physical activity will influence risk of recurrent vascular events in stroke survivors.

See bmj.com for details of the ExStroke Pilot Trial Group.

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Effect of unsupervised home based proprioceptive training on recurrences of ankle sprain: randomised controlled trial

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ABSTRACT

Objective To evaluate the effectiveness of an unsupervised proprioceptive training programme on recurrences of ankle sprain after usual care in athletes who had sustained an acute sports related injury to the lateral ankle ligament.
Design Randomised controlled trial, with one year follow-up.
Setting Primary care.
Participants 522 athletes, aged 12-70, who had sustained a lateral ankle sprain up to two months before inclusion; 256 (120 female and 136 male) in the intervention group; 266 (128 female and 138 male) in the control group.
Intervention Both groups received treatment according to usual care. Athletes allocated to the intervention group additionally received an eight week home based proprioceptive training programme.
Main outcome measure Self reported recurrence of ankle sprain.
Results During the one year follow-up, 145 athletes reported a recurrent ankle sprain: 56 (22%) in the intervention group and 89 (33%) in the control group. Nine athletes needed to be treated to prevent one recurrence (number needed to treat). The intervention programme was associated with a 35% reduction in risk of recurrence. Cox regression analysis showed significantly fewer recurrent ankle sprains in the intervention than in the control group. This effect was found for self reported recurrent ankle sprains (relative risk 0.63, 95% confidence interval 0.45 to 0.88), recurrent ankle sprains leading to loss of sports time (0.53, 0.32 to 0.88), and recurrent ankle sprains resulting in healthcare costs or lost productivity costs (0.25, 0.12 to 0.50). No significant differences were found between medically treated athletes in the intervention group and medically treated controls. Athletes in the intervention group who were not medically treated had a significantly lower risk of recurrence than controls who were not medically treated.
Conclusions The use of a proprioceptive training programme after usual care of an ankle sprain is effective for the prevention of self reported recurrences. This proprioceptive training was specifically beneficial in athletes whose original sprain was not medically treated.
Trial registration ISTRCN34177180

WHAT IS ALREADY KNOWN ON THIS TOPIC

Ankle sprains are the most common injuries in various sports
Proprioceptive training reduces recurrences in ankle sprain by 50%
Despite treatment of an ankle sprain, risk of recurrence remains high

WHAT THIS STUDY ADDS

An unsupervised home based proprioceptive training programme prevents self reported recurrences of ankle sprain in acutely injured athletes
Nine people need to be treated to prevent one recurrence
Proprioceptive training is a useful addition to usual care, specifically in athletes who did not have medical treatment for their ankle sprain

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INTRODUCTION

There is strong evidence that in the year after injury, athletes have twice the risk of a recurrent ankle sprain.[1-4] Although treatment of ankle sprain aims at recovery, it does not seem to lower the increased risk of re-injury.[5] We evaluated the effectiveness of an individual home based proprioceptive training programme, after rehabilitation and treatment by usual care, to prevent ankle sprain recurrences.

METHODS

The randomised controlled trial had a follow-up of one year because the increased risk for ankle sprain

recurrences seems to exist only during the first year after injury.[1-4] Athletes were randomised to intervention or control, with stratification for sex, type of enrolment, and usual care of ankle sprain.

Athletes were recruited from August 2006 to August 2007 through medical channels (11 emergency rooms, five general practices, and four physical therapy offices) throughout the Netherlands and non-medical channels (adverts in newspapers, sports magazines, sports tournaments, and on the internet). All were active sports participants aged 12-70 who had sustained an ankle sprain in the preceding two months.

Before inclusion, a physical therapist contacted each injured athlete by phone and completed an injury registration questionnaire.[6] This included questions on diagnosis, cause, and aetiology of the injury. If the injury had been medically treated, the advised treatment and profession of who treated the injury were recorded.

All participants received treatment according to usual care, defined as any form of rehabilitative treatment used by the athlete. Athletes allocated to the intervention group were informed that they would also receive an eight week proprioceptive training programme.

Intervention

The training programme is shown in the appendix on bmj.com. It prescribed three training sessions a week, for a maximum of 30 minutes a session. Athletes were encouraged to perform the exercises as part of their normal warm up. Exercises gradually increased in difficulty and training load during the eight week programme. The intervention group received a balance board, exercise sheets, an instructional DVD, and details of a website with all the information (accessible only for those in the intervention group).

Outcome measures

The outcome was expressed as incident ankle sprains per 1000 hours of exposure. We differentiated self reported sudden inversions of the same ankle according to severity[7]: recurrences leading to loss of sports time and recurrences resulting in healthcare costs or lost productivity costs, or both.

Exposure and injury registration

During the one year follow-up, athletes reported recurrences and details of their sports participation for each training session and match on a monthly basis. Athletes who reported a recurrence completed a web based questionnaire. Athletes who had sustained a recurrence also received a cost diary that registered all healthcare costs and costs due to loss of productivity from the moment of injury until full recovery.

Athletes in the intervention group self rated compliance after four weeks and eight weeks of training. To rule out contamination between groups, every month we asked those in the control group whether they had participated in proprioceptive training during the past month. A physical therapist and the primary researcher, blinded to group allocation, independently rated all registered ankle injuries as acute lateral ankle sprains or other ankle injuries. See bmj.com.

From our sample size calculation we needed 275 people per group to detect a clinically relevant effect.

Statistical methods

We calculated the number of recurrent ankle sprains reported per 1000 hours of sports, with exposure time of each individual player until the first recurrent ankle sprain. We also carried out a subgroup analysis on medical care for the inclusion ankle sprain. Cox regression analysis compared risk of recurrence of ankle sprain between the groups, with adjustment for age, type of sport (contact or non-contact), and level of sports (competitive or recreational).

RESULTS

We recruited 522 athletes, 351 (67%) through medical channels and 171 (33%) through non-medical channels. Stratification ensured equal numbers for key factors in the intervention (n=256) and control group (n=266), and at baseline there were no significant differences between groups. See bmj.com. The dropout rate was similar between groups. Five out of 266 athletes in the control group (2%) reported performing some sort of proprioceptive training exercises during follow-up.

Exposure and injury characteristics

Participants took part in 30 140 hours of sports in the intervention group and 30 682 hours in the control group. During the one year follow-up, 145 (28%) athletes reported a recurrent ankle sprain: 56/256 (22%) in the intervention group and 89/266 (33%) in the control group. The overall incidence of ankle sprain per 1000 hours of sports was 1.86 (95% confidence interval 1.37 to 2.34) in the intervention group and 2.90 (2.30 to 3.50) in the control group (table).

Significantly lower relative risks for self reported recurrences of ankle sprain, time loss, and costs were found for the intervention athletes. Nine athletes need to be treated to prevent one ankle sprain recurrence. Furthermore, the programme led to a 35% relative risk reduction in the intervention group.

Effect on medically and non-medically treated athletes

Cox regression subgroup analysis was carried out for ankle sprains that included medical treatment during usual care at time of inclusion. Within this subgroup, we found an intervention effect only for recurrences leading to costs (0.24, 0.08 to 0.72).

Incidence of injury (95% confidence interval) per 1000 hours of participation in sports and relative risk (RR) by injury severity variables and allocated group

Ankle sprain	Intervention	Control	RR*
Self reported	1.86 (1.37 to 2.34)	2.90 2.30 to 3.50)	0.63 (0.45 to 0.88)
Time loss	0.65 (0.38 to 0.92)	1.17 (0.82 to 1.52)	0.53 (0.32 to 0.88)
Leading to costs	0.29 (0.11 to 0.47)	1.08 (0.74 to 1.42)	0.25 (0.12 to 0.50)

*Derived from Cox regression adjusted for age, type of sport, and level of sports.

The intervention group athletes who reported non-medical treatment of their ankle sprain had a significantly lower risk of recurrence than controls. This effect was found for self reported recurrences (0.45, 0.28 to 0.72), for recurrences leading to loss of sports time (0.47; 0.23 to 0.96), and for recurrences leading to costs (0.25; 0.10 to 0.61).

Compliance with the programme

A total of 58 (23%) athletes in the intervention group said they had fully complied with the eight week proprioceptive training programme; 75 (29%) said they had been partially compliant; 89 (35%) were classified as not compliant. Compliance with the training programme was unknown for 34 (13%) athletes. Five out of 266 in the control group (2%) said they had performed some sort of proprioceptive training exercises during the one year follow-up, and were not incorporated in the analysis.

DISCUSSION

An unsupervised home based proprioceptive training programme given in addition to usual care is effective in reducing the incidence of recurrent ankle sprains in athletes. We found a twofold reduction in risk of recurrence for self reported recurrences, and time loss because of recurrences. Other proprioceptive training trials have recently shown a reduction in the incidence of ankle sprain recurrence.[6 8] Ankle sprains leading to costs were 3.6 times higher in control athletes than in intervention athletes.

Study limitations

We used self reports for recording the initial ankle sprain and for recurrent ankle sprains. As recurrences were reported on a monthly basis, recall bias was not likely. Misclassifications of injuries sustained during the follow-up, however, was possible. We used registration forms to minimise classification errors.[6] Assessors were blinded to group assignment. Loss to follow-up, at 14%, was considerably lower than the expected 20%. Baseline variables of athletes that were lost to follow-up did not differ significantly from the other athletes.

Relation to other studies

Only one other randomised controlled trial has studied the effect of a rehabilitative training programme on risk of recurrence of ankle sprain after an acute ankle ligament sprain.[9] A year after injury, it found a significant difference in re-injuries in favour of the intervention group. However, the sample size was small, more athletes were lost to follow-up, information on re-injuries was collected retrospectively and exercises were supervised by physical therapists.

Generalisability

As the intervention was implemented for both sexes, all ages, all types of sports, and at different levels of sports, young elite to intermediate and recreational senior athletes would benefit from using the presented training programme for the prevention of recurrences of ankle sprain. By including non-medically treated and medically treated athletes, we covered a broad spectrum of injury severity. This suggests that the present training programme can be implemented in the treatment of all athletes. Furthermore, as it is reasonable to assume that ankle sprains not related to sports are comparable with those in sports, the programme could benefit the general population.

Contributors: See bmj.com.

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Competing interests: None declared.

Ethical approval: The study was approved by the medical ethics committee of the VU University Medical Center, Amsterdam, Netherlands. All athletes gave individual informed consent. Additional parental informed consent was given for athletes under the age of 18.

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What's the BM?

"What are the patient's BMs doing?" we ask. "The BMs are really high!"

The preferred term is capillary blood glucose, rather than BM, which is medical slang. Literally it stands for Boehringer Mannheim, a German pharmaceutical company that used to make by far the most commonly used test strips for blood glucose. Thus, when doctors or nurses referred to a blood sugar result they said that the patient's BM was so many millimoles. This also meant that the measurement had been carried out using a quick finger prick rather than a laboratory test. The name has stuck, even though the names of the test sticks used have changed.

Some diabetologists continue to use this terminology; others are less than happy.

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Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort

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ABSTRACT

Objective To assess the impairment in daily living activities in older people with age related changes in white matter according to the severity of these changes.
Design Observational data collection and follow-up of a cohort of older people undergoing brain magnetic resonance imaging after non-disabling complaints.
Setting 11 European centres.
Participants 639 non-disabled older patients (mean age 74.1 (SD 5.0), 45.1% men) in whom brain magnetic resonance imaging showed mild, moderate, or severe age related changes in white matter (Fazekas scale). Magnetic resonance imaging assessment also included cerebral infarcts and atrophy.
Main outcome measure Transition from no disability (defined as a score of 0 or 1 on the instrumental activities of daily living scale) to disability (score ≥2) or death over three year follow-up. Secondary outcomes were incident dementia and stroke.
Results Over a mean follow-up period of 2.42 years (SD 0.97, median 2.94 years), information on the main outcome was available for 633 patients. The annual rate of transition or death was 10.5%, 15.1%, and 29.5%, respectively, for patients with mild, moderate, or severe age related changes in white matter (Kaplan-Meier log rank test P<0.001). In a Cox model comparing severe with mild changes and adjusted for clinical factors of functional decline, the risk of transition to disability or death was more than twofold higher (hazard ratio 2.36, 95% confidence interval 1.65 to 3.81). The other predictors were age group, history of atrial fibrillation, and complaint of gait disturbances. The effect of severe changes remained significant independently of baseline degree of atrophy and number of infarcts. Incident stroke and dementia only slightly modified this effect.
Conclusion The three year results of the LADIS study suggest that in older adults who seek medical attention for non-disabling complaints, severe age related changes in white matter independently and strongly predict rapid global functional decline.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Age related changes in white matter are often detected by neuroimaging in older people

Such changes are associated with cognitive deficits, depression, motor abnormalities, and urinary dysfunction, all of which contribute to disability in older people

WHAT THIS STUDY ADDS

Older people with extensive age related changes in white matter are at high risk of functional decline over the next three years

The annual rate of death or disability was 10.5%, 15.1%, and 29.5%, respectively, for patients with mild, moderate, or severe changes in white matter

With severe changes in white matter prognosis was only slightly worsened by incident stroke and dementia

INTRODUCTION

Many older people have age related changes in white matter on brain magnetic resonance imaging. Such changes, also called leukoaraiosis,[1] are of moderate to severe grade in about a third of cases.[2] There have been no studies of adequate power primarily aimed at assessing such changes and their severity in relation to daily living disability.

Both prevalence and severity of age related changes in white matter increase with age, and several dysfunctions occurring with age and contributing to disability have been reported to be associated with such changes, raising the hypothesis that they might be one of the processes causing disability in older people. We need to establish their net contribution in relation to other factors of disability. We do not know what grade of changes produces functional effects and whether there is a dose-effect or a threshold relation between the severity of changes and the risk of functional decline.

The LADIS (leukoaraiosis and disability) study is a multicentre European collaboration to investigate whether age related changes in white matter are an independent determinant of functional decline in older people. We present the three year follow-up results of the study from a cohort of older people undergoing brain magnetic resonance imaging after non-disabling complaints.

METHODS

End point definition

Our primary end point was transition to disability, based on Lawton and Brody's instrumental activity of daily living scale (IADL)[3] as the change from a score of 0 or 1 at baseline to a score of 2 or more or death. Secondary outcomes were incident dementia and stroke.

Patients

Participants were patients aged 65-84 in whom age related changes in white matter of any degree were found when they were being investigated at one of

the 11 European centres for complaints such as mild memory or motor problems, minor cerebrovascular events, and mood alterations, none interfering with common activities of daily living. To be included, patients had to perform without help in every activity of the instrumental activities of daily living scale or limited in only one activity.

Out of the 897 consecutive patients screened for inclusion, 180 (20%) were excluded leaving 717 eligible patients. Seventy eight of the eligible patients refused to participate, and 639 (71% of the screened sample) were finally enrolled in the study.

Assessment

Entry assessment included a detailed magnetic resonance imaging study and several functional and clinical measures.[4] Patients were asked to undergo yearly clinical and functional assessments for a maximum of three years. At entry and at each follow-up visit, a structured questionnaire was used to assess health, depression, gait disturbances, falls, visual impairment, and hearing loss.

Our outcome variable was no limitation versus limitation of any degree in one or more of the eight tasks in the IADL scale. All participants underwent magnetic resonance imaging following a standard protocol.

A blinded central rater used the visual Fazekas scale to rate severity of age related changes in white matter at baseline.[5] Patients were subdivided into three severity groups: grade 1 (mild changes); grade 2 (moderate changes); and grade 3 (severe changes). A single rater measured the volume of white matter changes. We assessed several magnetic resonance imaging variables as possible confounders of outcome in our study.

Statistical analysis

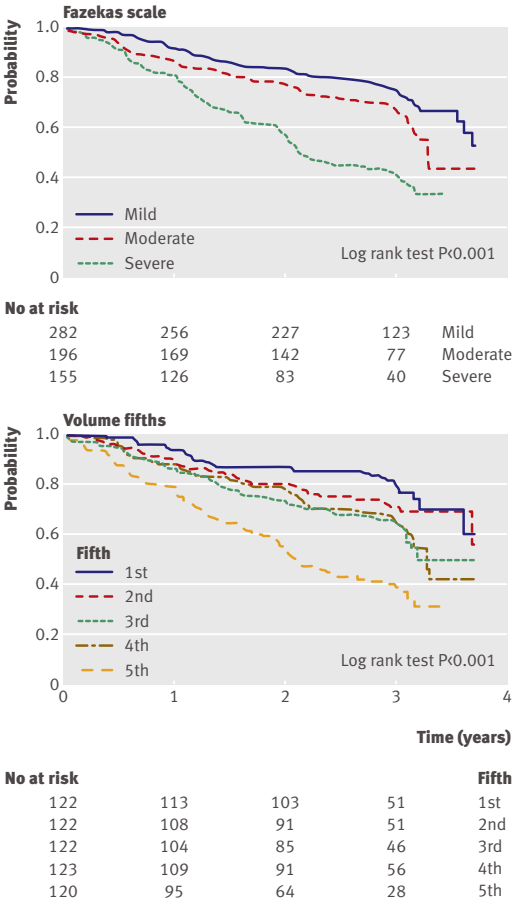
We examined variations of baseline demographics, risk factors, and comorbidities across the three severity groups. We calculated the incidence rate of transition to disability or death and stroke and dementia in each of the three severity groups. The Kaplan-Meier curves examined the probability of surviving free of disability or death across the severity groups. We estimated differences between groups.

With the mild group taken as reference,[4] we compared the net predictive effect of Fazekas grades on the primary end point in the severe and moderate groups with Cox regression analysis, controlling for potential confounders. In a further model, we controlled for the effect of age related changes in white matter on transition, including magnetic resonance imaging infarcts and atrophy.

During the follow-up period 242 patients reached the primary end point and 391 did not and were censored. Of these, 60 remaining patients were retained as still potentially informative. Baseline factors did not differ significantly between these two groups.

RESULTS

At follow-up, of the 639 patients (mean age 74.1 (SD 5.0) years, 45.1% men) enrolled, we had information about vital and instrumental activities of daily living status for 633 (99.1%) (mean age 74.1 (SD 5.0) years, 45.0% men). Among these patients 44% had mild, 31% had moderate, and 25% had severe age related changes in white matter. Older age, history of arterial hypertension, stroke, falls in the past year, complaint of gait disturbances, and visual problems were all more common among patients with the severe grade.



Kaplan-Meier probability of survival free of transition from independence in instrumental activities daily living to disability or death according to baseline severity grades in age related changes in white matter

Over a mean follow-up period of 2.42 years (SD 0.97, median 2.94 years), 242 (38.2%, mean age 75.4 (SD 4.8), 44.2% men) of the 633 patients reached the study end point. Patients with severe age related changes in white matter had a worse prognosis; about 60% had become disabled or had died at the end of the follow-up.

The rate (per 100 person years at risk) of transition from independence in instrumental activities of daily living activities to disability or death was 10.5 (95% confidence interval 8.2 to 12.8), 15.1 (11.6 to 18.6), and 29.5 (23.5 to 35.5) for patients in the mild, moderate, and severe Fazekas scale group, respectively. Survival analysis carried out for each of the Fazekas scale grades or volume fifths (figure) showed that the probability of surviving free of disability or death decreased with the increasing severity of changes in white matter (Kaplan-Meier log rank test $P<0.001$ for either grading). When we compared the moderate

with the severe group, and the fourth with the fifth group, median survival times were 3.27 (3.16 to 3.38) *v* 2.14 (1.67 to 2.62) and 3.27 (3.12 to 3.42) *v* 2.09 (1.72 to 2.47) years, respectively.

When we compared the severe with the mild grades of changes and adjusted for confounders by Cox analysis (table), the hazard of transition to disability or death was more than twofold higher for the severe Fazekas group.

When we analysed fifths of volume of age related changes in white matter with adjustment for confounders, the hazard of transition to disability or death was almost threefold higher (hazard ratio 2.99, 1.77 to 5.05) comparing the highest fifth with the lowest.

When we considered as outcome the transition to disability alone (excluding death), the adjusted hazard ratios were 1.09 (0.74 to 1.59) for patients with moderate changes and 2.50 (1.72 to 3.65) for those with severe changes, in comparison with the mild group.

Evidence of multiple lacunar infarcts and non-lacunar infarcts and severity of atrophy on magnetic resonance imaging at baseline was also significantly associated with the degree of severity of age related changes in white matter. When we added these variables to the Cox model, together with the three severity grades and all other confounders, severe changes remained an independent predictor of transition to disability or death (hazard ratio 2.36, 1.55 to 3.60).

Severity grades of age related changes in white matter independently predicted the severity of functional decline as expressed by the mean number of instrumental activities of daily living changed by follow-up (1.09 (SD 1.99) in the mild, 1.42 (SD 2.0) in the moderate, and 2.53 (SD 2.69) in the severe group; P<0.001 after adjustment for confounders). The activities most commonly limited among patients with functional decline were housekeeping, shopping, and mode of transportation

In the mild, moderate, and severe change groups, the rate (per 100 person years at risk) of incident stroke was 1.8 (95% confidence interval 0.8 to 2.8), 3.2 (1.6 to 4.9), and 6.9 (4.0 to 9.8), and the rate of incident dementia was 3.2 (1.9 to 4.5), 4.7 (2.8 to 6.6), and 12.8 (8.9 to 16.6), respectively. Adding incident stroke and dementia to the Cox regression model only slightly attenuated the effect of severe changes on transition to disability or death (hazard ratio 2.06, 1.40 to 3.04).

Effect of severity of age related changes in white matter and other independent predictors of transition from independence in instrumental activities daily living to disability or death*

	Hazard ratio (95% confidence interval)	
	Unadjusted	Adjusted†
Fazekas grade:		
Mild	1	1
Moderate	1.48 (1.08 to 2.05)	1.13 (0.79 to 1.61)
Severe	3.01 (2.22 to 4.08)	2.36 (1.65 to 3.81)
Age group (years):		
65-69	1	1
70-74	1.77 (1.20 to 2.62)	1.73 (1.14 to 2.64)
75-79	2.19 (1.49 to 3.22)	1.91 (1.23 to 2.97)
80-84	2.61 (1.71 to 3.99)	2.24 (1.35 to 3.70)
Baseline instrumental activities of daily living=1	3.69 (2.83 to 4.81)	3.08 (2.24 to 4.23)
Atrial fibrillation	2.04 (1.38 to 3.01)	1.69 (1.09 to 2.64)
Complaint of gait disturbances	1.97 (1.52 to 2.54)	1.62 (1.16 to 2.52)
History of osteoarthritis	0.80 (0.60 to 1.08)	0.58 (0.40 to 0.83)
Education (per year of schooling)	0.94 (0.91 to 0.97)	0.90 (0.86 to 0.94)

*Variables in models were age, sex, education, baseline instrumental activities of daily living (0 *v* 1), centre, living condition, body mass index, pulse pressure, history of ischaemic heart disease, heart failure, hypertension, atrial fibrillation, diabetes, depression, falls, osteoarthritis, stroke, chronic obstructive pulmonary disease, peripheral vascular disease, gait, urinary, visual, or hearing disturbances. Analysis stratified for reason for referral.
†Cox regression models, adjusted for multiple factors of disability.

DISCUSSION

Principal findings

In an older person undergoing brain magnetic resonance imaging after a non-disabling complaint, the presence of severe age related changes in white matter predicts a more rapid decline in global functioning, independent of age and several factors known to be associated with disability in older people. This effect does not seem to be related to baseline cerebral atrophy or infarcts, nor is it consequent on incident strokes. Part of the effect is explained by incident dementia, but the influence of severe changes on disability does not depend exclusively on their ability to determine dementia. Concerning the hypothesised dose-effect relation between severity grades and the probability of transition or death, while the predicted number of instrumental activities of daily living impaired would support the hypothesis, the analysis of primary outcome by fifths of volume of changes, showing the remarkable increased risk for the highest fifth, corroborates the hypothesis of a threshold effect.

Strength and limitations of the study

A main limitation to the generalisability of our results is related to the hospital based design and the recruitment of patients from several different clinical centres, both possible sources of bias linked with referral and selection. Nearly all patients were enrolled after seeking medical attention and therefore no inference can be made to subjects with age related white matter changes who are free of symptoms.

As in previous studies, we used the instrumental activities of daily living scale. The reliability and validity of such a scale is considered sufficient to warrant its use in clinical situations.[6]

Conclusions and policy implications

Previous studies have consistently shown that age related changes in white matter predict decline in motor performance,[7] onset of dementia,[8] and deterioration in selective cognitive domains.[9] No study has hitherto addressed the question of whether such changes are the direct determinant of

functional dependence in older people. Providing an answer to this question might indicate potential targets for intervention to prevent or slow down the process.

Age related changes in white matter are thought to develop from repeated ischaemic insults to subcortical brain areas, mainly caused by small vessel disease.[10] From the histological point of view, these hyperintense lesions on magnetic resonance imaging correspond to areas characterised by loss of myelinated fibres and gliosis without frank tissue necrosis,[11] consistent with the concept of incomplete infarction.[12] The currently accepted view is that these age related changes are a marker of small vessel disease associated with arterial hypertension and other vascular risk factors.

Our observations might provide clinicians with specific evidence to support the use of neuroimaging as an additional investigation of functional decline in older people. No conclusive evidence has been reached as yet about interventions that could favourably alter the development of disability in such patients. Preliminary studies indicate that treating hypertension might slow the progression of age related changes in white matter.[13] Therapeutic trials should include global functioning among the main outcome measures.

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Competing interests: None declared.

Ethical approval: The study protocol was approved by each centre's ethics committee.

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We welcome submission of any trial of a drug or device that asks an original research question that will sufficiently aid doctors' decisions. This is most likely to be a trial that directly compares a new drug or device (or new regimen or indication) with the best current treatment(s) using clinically valid doses or administration of both study and comparator interventions. Placebo controlled trials often have much more limited relevance to practice than head to head trials and may not sufficiently help *BMJ* readers' decisions, but we welcome emailed presubmission inquiries about these too.

We will give priority to a drug or device trial if it

- Has a main outcome measure that's sufficiently clinically relevant and, if it's a composite outcome, matters enough to patients
- Has important results: please note that we welcome "negative" trials as long as their research questions are important, new, and relevant to general readers, and their designs are appropriate and robust
- Is reported fully in line with the CONSORT statement or the relevant CONSORT extension statement and has sufficient internal and external validity
- Is submitted with the original study protocol, for use in confidence during peer review
- Is reported transparently, as explained in our detailed advice below on reporting industry sponsored trials
- Is a phase III, IIIb, or IV trial. Trials done for "label extension" may be useful to *BMJ* readers if they ask research questions that are sufficiently new and relevant to practice.

If you are submitting a report of such a clinical trial please follow all the good publication practice (GPP) guidelines and the European Medical Writers Association (EMWA) guidelines on properly reporting the role of professional medical writers. Please provide the trial registration details, declare the details of all sources of funding for the study, provide statements of competing interests and contributorship, fully describe the role of the study sponsors, provide a statement on the independence of researchers from funders, and state whether all authors had full access to and can take responsibility for the data and analyses. All of these items are explained at http://resources.bmj.com/bmj/authors/types-of-article/research.

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Effectiveness of quinine versus artemether-lumefantrine for treating uncomplicated falciparum malaria in Ugandan children: randomised trial

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EDITORIAL
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STUDY QUESTION What is the effectiveness of oral quinine compared with that of artemether-lumefantrine in treating uncomplicated malaria in children?

SUMMARY ANSWER The effectiveness of a seven day course of quinine for the treatment of uncomplicated malaria in Ugandan children was significantly lower than that of artemether-lumefantrine.

Design

This was an open label randomised effectiveness study. Participants were randomly assigned to receive oral quinine or artemether-lumefantrine. Block randomisation was used with blocks of 20. Computer generated randomisation codes were prepared independently and put in sequentially numbered opaque sealed envelopes, which were assigned in sequential order to participants after inclusion. Participants in the quinine arm received a seven day course of quinine sulphate as 10 mg/kg body weight per dose three times daily, provided as 300 mg tablets (Rene Pharmaceutical, Kampala, Uganda). Participants in the artemether-lumefantrine arm received WHO recommended weight specific artemether-lumefantrine blister packs (Coartem; Novartis Pharma, Basel, Switzerland).

Participants and setting

Overall, 175 children aged 6 to 59 months were recruited from the outpatient clinic at Uganda's national referral hospital, Mulago, in Kampala. Inclusion criteria were an axillary temperature of ≥37.5°C or a history of fever in the past 24 hours, microscopically confirmed *Plasmodium falciparum* mono-infection with any density of asexual parasites, ability to tolerate oral therapy, and no history of antimalarial drug intake in the preceding two weeks. Children were not recruited if they met at least one of several exclusion criteria: a history of allergy to quinine or artemether-lumefantrine, evidence of severe malaria or other concomitant febrile illness, or residence more than 20 km from the health clinic.

Primary outcome(s)

Primary outcomes were parasitological cure rates after 28 days of follow-up unadjusted and adjusted by genotyping to distinguish recrudescence from new infections.

Main results and the role of chance

Cure rates were significantly higher in the artemether-lumefantrine group than in the quinine group. Using survival analysis, cure rates unadjusted by genotyping were 96% for the artemether-lumefantrine group and 64% for the quinine group (P<0.001). Participants were 10 times more likely to fail treatment with oral quinine than with artemether-lumefantrine (hazard ratio 10.7, 95% confidence interval 3.3 to 35.5, P=0.001). The risk of treatment failure unadjusted by genotyping was significantly higher in the quinine group than in the artemether-lumefantrine group (35.3%, 95% confidence interval 25.6% to 47.4% *v* 4.1%, 1.3% to 12.0%): risk difference 31.3% (19.4% to 31.1%, P<0.001).

Harms

No harms were identified in this study.

Bias, confounding and other reasons for caution

Serum levels of quinine were not measured, and so adherence measures depended on care givers' reports and pill counts, which may have been inaccurate. It remains unclear if our inability to fully explain the poor effectiveness of quinine resulted from limitations in our assessment of compliance or was due to other factors.

Generalisability to other populations

Our study was carried out in an area of medium to high malaria transmission and in a population that is at highest risk for malaria, highlighting the importance of these findings in similar populations.

Study funding/potential competing interests

This study received funding from the Department for International Development, UK, through the Malaria Consortium (contract No CNTR 04 5432). The authors declare no potential competing interests.

Trial registration number

ClinicalTrials.gov NCT00540202.

COMPARATIVE EFFECTIVENESS OF ORAL QUININE AND ARTEMETHER-LUMEFANTRINE AT DAY 28

Outcome	Risk of failure (95% CI)		Risk difference (95% CI)	P value
	Quinine group (n=86)	Artemether-lumefantrine group (n=89)		
Treatment failure (%)*	35.3 (25.6 to 47.4)†	4.1 (1.3 to 12.0)†	31.3 (19.4 to 31.1)	<0.001
Treatment failure (%)‡	23.1 (14.9 to 35.0)§	0§	23.1 (13.2 to 33.1)	<0.001

*Any early treatment failure, late clinical failure, or late parasitological failure
†Unadjusted by genotyping
‡Any early treatment failure, late clinical failure, or late parasitological failure caused by recrudescence
§Adjusted by genotyping