6 minutes assisted leg and arm cycling test: feasibility, validity, test-retest responsivity and responsivity in patients with neuromuscular and metabolic disorders

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2.1 Primary Objectives: 1) To test the feasibility of the six minute assisted leg and arm cycling test in patients aged 6-18 years with Duchenne muscular dystrophy (DMD), Beckers muscular dystrophy (BMD), Limb Girdle muscular dystrophy (LGMD),...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON35872

Source
ToetsingOnline

Brief title
Assisted 6-minute cycling test in neuromuscular and metabolic disorders

Condition

- Musculoskeletal and connective tissue disorders congenital
- Inborn errors of metabolism
- Neuromuscular disorders

Synonym
congenital neuromusclar disease, muscle diseases

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: AGIKO salaris Saskia Koene,Energy4all; Tjallingh Roorda Foundation?;Duchenne Parent Project

Intervention

Keyword: cycling test, metabolic disease, neuromuscular disease, outcome measures

Outcome measures

Primary outcome

Percentage of successful tests (see definition in Chapter 2): feasibility

Number of revolutions cycled in 6 minutes on the Dynamic bicycle: good to

strong correlation between endurance and function status (MFM).

Secondary outcome

Number of revolutions cycled at 1, 2, 3, 4 and 5 minutes on the Dynamic bicycle

Test- retest values (number of revolutions) for the A6MCT within two weeks

(arms and legs)

Responsivitiy of the A6MCT and the correlations with the 6MWT, timed tests and

the MFM over one year

EMG during the cycling on the Dynamic bicycle (only in patients)

Heart rate (beats/min) during the cycling on the Dynamic bicycle

Subjective fatigue (OMNI) during the cycling on the Dynamic bicycle

Distance (m) walked in 6 minutes

Timed up and go tests:

*Time (s) to walk or run 10 meters

*Time (s) to stand up from the floor

*Brooke and Vignos scale

Gender

Age

Height

Body weight

Study description

Background summary

More and more clinical studies are performed in neuromuscular disorders, mostly using rational therapies based on thorough knowledge of the pathophysiology and molecular alterations.

To see the effect of these experimental interventions on the patient*s health status, it is important to have reliable outcome measures. Functional outcome measures reflect the functional abilities of the patient in daily life. These outcome measures may be questionnaires, timed tests, dexterity tests and exercise tests. Since exercise capacity is the most widely used functional outcome in current clinical trials for neuromuscular and metabolic disorders 1 and endurance is in our opinion very sensitive to general disease progression, it is important to validate feasible and sensitive exercise capacity outcomes that are responsive to change.

In adults, the gold standard for measuring exercise capacity is an incremental workload exercise test on an electronically braked, pedal rate-independent cycle ergometer to measure peak working rate, parallel measuring oxygen consumption and heart rate. In young or diseased children, this test is not feasible and too burdensome. In addition, since most daily activities are performed at submaximal levels of exertion, it has been proposed that submaximal functional test are a better reflection of physical capacity and the ability to perform the activities of daily life 2.

Currently, the 6-minute walking test (6MWT) is the most used measure to test exercise tolerance. In this test, children are asked to walk (not run) as far as possible in 6 minutes. The test has a high correlation with the standardized maximum incremental exercise testing on a treadmill 2 in healthy adolescents, and with aerobic fitness in healthy schoolchildren 3. The 6MWT also correlates

with aerobic fitness in children with Cystic Fibrosis 3 and had a high reproducibility in boys with Duchenne Muscular Dystrophy (DMD) 4. However, even ambulatory boys had a high likelihood of falls. Besides the risk of injuries during the challenging test, most children with neuromuscular or mitochondrial disorders are wheel chair bound or won*t be able to walk safely for 75 meters. Above this in most children with neuromuscular disorders osteoporosis is present with an increased risk of fractures while falling. This will limit the amount of subjects to be included in studies using the 6MWT as an outcome measure.

We developed an assisted 6 minutes cycling test (A6MCT) for arms and legs. This test is also feasible for wheel chair bound patients. And, since it is an assisted test, it is also suitable for patients who are not able to do a normal cycling test, because of muscle weakness, hypotonia or severe exercise intolerance. Heart rate and subjective level of fatigue are monitored and to exclude bias from behaviour-tiredness and lack of motivation, the level of fatigue is measured by surface EMG. Heart rate is also used for safety monitoring. The a6MCT was validated in healthy boys aged 6-12 years of age and compared to boys with DMD. In this study with healthy boys and in boys with DMD, the a6MCT validity was good, repoducability was high and the test was feasible and reliable for boys with DMD.

Since there is no gold standard for exercise capacity in children, we take the 6MWT because it is the most widely used test with a very good reliability and a good correlation with the gold standard for exercise capacity in adults. Therefore, we will correlate the distance walked in the 6MWT with the number of revolutions on the A6MCTleg/arm to validate the A6MCT. A disadvantage of choosing this test, is that we can only include ambulatory patients which are able to walk safely for 75 meters. We use several other functional (secondary) outcome measures to create a broader picture of the (dis)abilities of the patients, which is interesting in interpreting the value of the A6MCT for the general functional status of the patients. Especially the Motor Function Measure is a well defined test of motor functions, not disease specific but developed for disorders with flaccid paresis, and proven valid and sensitive for change. Sample sizes are calculated per disease, using the percentage of predicted achievement on the 6MWT and the expected variance to predict the number of children needed. Since there is a widely used test to follow-up on patients with patients with Friedreich Ataxia, namely the FARS (no gold standard), we also perform this test in this group.

We choose to include a diverse pallet of diseases in our study. The main groups are the muscular dystrophies and the mitochondrial disorders (including Friedreich Ataxia (FRDA)). We also chose to include patients with Congenital Disorders of Glycosylation (CDG), another multisystem disease with muscle weakness, hypotonia and mild exercise intolerance. All diseases included in this study are rare diseases, all of main interest in our centre. None of the groups have adverse effects of exercise, other than tiredness and (possible)

muscle pain.

1.1 Goals and hypotheses

In this study, we aim to test the feasibility of the assisted six-minute bicycle test in several groups of patients with neuromuscular and metabolic disorders. Since the bicycle test is assisted, we hypothesize that the test is feasible in children with severe muscle weakness or exercise intolerance. We also hypothesize that in six minutes, a difference between the muscle weakness and exercise intolerance will be revealed, without challenging to children with exercise intolerance too much. In previous studies in healthy boys and boys with DMD, the a6MCT has already shown to be feasible and therefore we hope that the test will also be feasible in young children and children with cognitive impairment or mild behavioural problems, since part of the tested boys had comparable problems.

We also aim to test the validity of the test in the various groups of children with neuromuscular and metabolic diseases. The validation however, is a difficult part of the study, since there is no gold standard to measure endurance or exercise capacity in children, nor a gold standard to measure disease severity in any of the diseases. Since the six-minute walking test is a valid and widely-used outcome measure for exercise capacity in children, we use this test as a reference for the validation of the six minute assisted bicycle test. A previous study has already shown that the A6MCT is positively correlated to the 6MWT in healthy boys (manuscript in preparation). A small sample of three boys with DMD, who performed the 6MWT and a6MCT, showed the same trend. This limits our study population, since we can only investigate ambulatory patients. To be able to recruit enough patients, we chose to have at least 50% ambulatory patients in our population. Secondary, we will also correlate the findings at the six minute assisted cycling test with the widely-used timed up and go tests, disability tests and the Motor Function Measure. The Motor Function Measure is the most reliable and widely used outcome measure in children with flaccid paresis and proven valid for various neuromuscular and metabolic disorders. All tests (6 minutes bicycling test with arms and legs, the 6 minute walking test and the timed up and go test) are also performed in stratified selected healthy girls aged 6-16 years and boys aged 13-16 years, since the data gathered at previous studies only include boys. We will support our validity tests with details about the neurophysiology and other parameters of endurance such as heart rate and subjective fatigue in patients with pure muscle weakness (e.g. DMD) and combined muscle weakness with profound exercise intolerance (mitochondrial disorders).

The test-retest reproducibility of the A6MCT will be assessed by repeating the test within two weeks. Since this might be a burden for some patients and their parents, this re-test is optional. Patients indicate after the first tests whether they will proceed with the repeat test. At this day, only the A6MCT will be repeated in patients with neuromuscular diseases since the other tests

have already been validated in this group. For the patients with metabolic disorders, all tests, except for the MFM will be repeated.

The responsivity will be tested within one year, since the MFM is valid for repetition within one year. At that day, all tests will be repeated, including timed tests, 6MWT and MFM.

The feasibility tests will be performed in eight diseases, either neuromuscular or metabolic diseases. The primary goal is to test the feasibility in either of these populations, it is only a secondary goal to compare between groups and to healthy individuals.

1.2 Relevance of the study

There is still no cure for Duchenne muscular dystrophy, Beckers muscular dystrophy, Limb Girdle muscular dystrophy, Myotonic dystrophy, Spinal Musclar Atrophy, Mitochondrial disorders, Friedreich ataxia, and Congenital Disorders of Glycosylation. Worldwide, there is a lot of effort being done to provide a cure for these rare diseases, but the lack of feasible and reliable outcome measures for non-ambulatory patients causes the number of included patients (and thus the power) in studies to be low. In this study, we aim to validate an outcome measure that is, in our opinion, a promising outcome parameter for neuromuscular diseases which limit muscle strength and endurance.

The scientific relevance will be high if the test proofs feasible and valid for one or more groups of patients included in this study. Since exercise capacity is one of the most important outcome measures for neuromuscular and (especially for) mitochondrial disorders, the assisted cycling test might be a promising primary outcome measure for future clinical trials. Many researchers around the world face the lack of valid functional outcome measures for non-ambulatory patients with neuromuscular or mitochondrial disorders. Especially since there are more and more clinical trials performed in these patient groups, there is a need for a feasible, valid, relevant and quantifiable outcome measure that is easy to perform and can be used internationally.

This study will also provide information on the fatigability of patients with neuromuscular disorders as well as reference values for children aged 6-18 years, both healthy and diseased. In boys with DMD there is a quite steady walking velocity at the 6 minute walking test 4. We expect the same results in the cycling test, which has been shown previously in healthy boys and boys with DMD.

The study will be conducted in children, since all disorders are most prevalent in childhood and severely impair children, already in their early teenage years. Moreover, we specifically aim to study the feasibility of this outcome measure in children since clinical trials in these diseases will also be performed in the pediatric population.

Study objective

2.1 Primary Objectives:

1) To test the feasibility of the six minute assisted leg and arm cycling test in patients aged 6-18 years with Duchenne muscular dystrophy (DMD), Beckers muscular dystrophy (BMD), Limb Girdle muscular dystrophy (LGMD), Myotonic dystrophy (MyoD), Spinal Muscular Atrophy (SMA) Mitochondrial disorders (MiD), Friedreich ataxia (FRDA), and Congenital Disorders of Glycosylation (CDG). The test is successful if the test is completed (cycling the full 6 minutes, possibly with pauses but restart within 15 seconds) without complications like pain or stifness.

a) To give a detailed description of the patients in which the A6MCT is not feasible (clinical condition; age; presence of spasticity, hypotonia, mental retardation, behaviour problems; why the test failed; MFM; 6MWT; timed tests).

2) To validate the six minute assisted leg and arm cycling test compared to the 6 minute walking test (widely accepted test for endurance in children) as a functional outcome measure in patients aged 6-18 years with healthy controls, DMD, BMD, LGMD, MyoD, SMA, MiD, FRDA and CDG if still ambulant. If the patients is non-ambulatory, we will use the MFM to test construct validity.

3) To determine the test-retest reproducibility and responsivity of the six minute assisted leg and arm cycling test in patients aged 6-18 years with DMD, BMD, LGMD, MyoD, SMA, MiD, FRDA and CDG.

2.2 Secondary Objectives:

1) To compare the number of revolutions on the A6MCTleg/arm, the objective (sEMG amplitude and frequency) and subjective fatigue, and the heart rate at 3 and 6 minutes of patients with neuromuscular disorders (muscle weakness) and mitochondrial disorders (exercise intolerance).

2) To correlate the number of revolutions on the A6MCTleg/arm to the Motor Function measure (lower extremity part).

3) To correlate the number of revolutions on the A6MCTleg/arm to the Motor Function measure (upper extremity part).

4) To obtain reference values for the six minute assisted leg and arm cycling test in healthy girls aged 6-18 years and healthy boys aged 13-16 years.

5) To correlate the number of revolutions on the A6MCTleg/arm to the Friedreich Ataxia Rating Scale (FARS) in patients with FRDA.

6) To compare the slope of the the number of revolutions on the A6MCTleg/arm between neuromuscular and metabolic diseases.

Study design

In this study, patients with various neuromuscular and metabolic disorders (DMD, BMD, LGMD, MyoD, MiD, FRDA and CDG) as well as healthy controls will be included.

3.1 Controls
Control girls and adolescent boys will be recruited by approaching local schools. If too many controls subscribe, a randomized subset will be drawn, stratifying for gender and age. After informed consent (see 8.2 Recruitment), patients are stratified randomized in two groups. First, they are asked to cycle on the Dynamic bicycle in 6 minutes (A6MCT), as far as possible, randomized for arms of legs first. There will be a pause of 15 minutes between arms and legs. In all children, heart rate will be monitored and subjective fatigue will be monitored. After a break of 30 minutes and a glass of lemonade, controls are asked to walk as far as possible in 6 minutes (6MWT). After a break of 10 minutes, the timed up and go and 10 meter walking test will be performed in both groups.

3.2 Patients
Patients will be recruited at our outpatient departments or via patients* organizations (see 8.2 Recruitment). Patients will be asked to come to our outpatient department. If the patient has a wheelchair for long distances, they are asked to use it to come to the outpatient clinic to decrease the possibility of fatigue on forehand. After informed consent, patients are included in the study. The Brooke and Vignos scale is filled in. Patients are stratified randomized in two groups, arms first or legs first. First, patients are asked to perform both A6MCTs. There will be a pause between the leg and arm tests of 15 minutes. Fatigue will be monitored by surface EMG to monitor fatigue in the thigh muscles, heart rate and a subjective fatigue scale. After a break of 30 minutes, the 6MWT is performed. In this test, it is allowed to rest against the wall but not to take a sit. After a break of 10 minutes, the timed tests and the MFM will be performed in both groups. The validation tests will also be performed in children in whom the A6MCT was not feasible, to define the group in which the A6MCT cannot be used.
With all tests, two researchers will be present to support the children and to catch them if they might fall during the 6MWT.

Both healthy controls and patients will be asked to call in case of serious adverse events, such as severe muscle pain or exhaustion. Patients will be called one week after the tests to ask for adverse effects of the exercise.

Study burden and risks

Children will not benefit from this study. However, for the future of therapeutic trials in children with neuromuscular and metabolic diseases, this study will be of great value. Since endurance is an outcome which is relevant to the patient and his quality of life, and it is a non-invasive outcome measure, it is a promising technique to be used in future clinical trials. The outcomes of this study can be used for advices concerning training in regular physiotherapy.
Since most patients we study don*t survive into adulthood or their functional abilities are quite different in adulthood compared to childhood, we depend on children to perform our study. In previous studies patients enjoyed the cycling test.
We don*t expect major risks in our study. Since we select patients who can safely walk for 75 meters, also the 6 minute walking test will be quite safe. However, there is always a risk of falling. Also, patients with severe cardiomyopathy are excluded. There are no serious adverse effects of short exercise in any of the groups, apart from tiredness and muscle pains. The effort of the exercises can be compared to playing outside or having physiotherapy. Since we select patients based on their ability to walk safely for 75 meters, we think they will walk further distances in daily life. Also, we try to prevent adverse effects of the exercises by regular pauses.
Patients are asked to come to the Rehabilitation outpatient clinic for three hours, if possible combined with another appointment in the hospital. The tests together take about 45 minutes in total, there is time to rest and have a drink between all tests.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Dependent on the disease, see paragraph 4.1 for more information.
General criteria:
6-18 years old

Exclusion criteria

Dependent on the disease, see paragraph 4.1 for more information.
General criteria:
Sever cardiomyopathy
Severe behavioural problems
High likelihood of falls
Hemiparesis

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-04-2012
Enrollment:	130
Type:	Actual

Ethics review

Approved WMO Date:	29-12-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-03-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL37246.091.11
Other	NTR: 1631