Personalized muscle training and biomarkers in children and adolescents with neuromuscular disease

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Primary Objective:1) To determine the efficacy of personalized progressive resistance training (PRT) on muscle strength of elbow flexors in children and adolescents with Spinal Muscular Atrophy and Congenital Myopathy compared to usual care...

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

Summary

ID

NL-OMON57017

Source
ToetsingOnline

Brief title
MAGNITUDE

Condition

- Musculoskeletal and connective tissue disorders congenital
- Muscle disorders

Synonym
muscle diseases, neuromuscular diseases

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Stichgting Spieren voor Spieren en Piet

Poortman fonds

Intervention

Keyword: biomarkers, neuromuscular diseases, resistance training, SMA

Outcome measures

Primary outcome

Objective 1 (primary outcome measure):

The change in maximal isometric strength of the elbow flexors (Newton) after 14 weeks progressive resistance training

Secondary outcome

Objective 2 (progressive resistance training + DMT versus usual care + DMT for SMA, progressive resistance training versus usual care for CM):

The change in maximal isometric strength of the elbow flexors (Newton) after 14 weeks progressive resistance training

Objective 3 (muscle profile):

At baseline functional, electrophysiological, morphological and metabolic parameters will be assessed on the basis of which an individual muscle profile is composed:

Function (Isokinetic Dynamometry)

• Isometric muscle strength (Newton, Newton/cm2) of the elbow flexors and elbow extensors

• Muscle power (watts) defined as average power during 5 isokinetic contractions of the elbow flexors and extensors

• Muscle endurance (seconds) measured with the dynamic IMPACT ergometer

Electrophysiological (High Density surface EMG)

• HD-EMG: root mean sqsuare (RMS) normalized to muscle activity during maximal isometric contraction, power spectrum analysis (e.g. median frequency (MF)), muscle fiber conduction velocity (MFCV), motor unit characteristics derived after decomposition (e.g. recruitment patterns, motor unit size, conduction velocity, etc.) 29-33. In addition, time until failure during the 60% of the maximal torque test will be measured.

Metabolic (Magnetic Resonance Spectroscopy)

• high-energy phosphate metabolites including ATP, PCr, Pi, and myofiber pH measured during (A) rest, (B) exercise, and (C) post-exercise.

Morphological (Magnetic Resonance Imaging)

• Muscle MRI: muscle fat fraction, muscle volume, contractile cross-sectional area (cCSA), muscle inflammation, and tissue architecture.

Objective 4 (clinical relevance)

• Goal Attainment Scaling (GAS) (score) on 1-3 personal goals

• Revised Upper Limb Score (total score)

• PROMIS global 02(R1)

• PROMIS fatigue SF (total score)

• PROMIS Upper Extremity SF (total score)

• Pittsburg Sleep Quality Index (total score)

Study description

Background summary

Progressive resistance (muscle strength- and muscle power-) training (PRST) is increasingly recommended in health care standards to combat disease progression in muscle disease. However, due to the lack of evidence on the efficacy of PRT, these recommendations remain vague and are therefore not easily translated into specific treatment of various muscle diseases.

Study objective

Primary Objective:
1) To determine the efficacy of personalized progressive resistance training (PRT) on muscle strength of elbow flexors in children and adolescents with Spinal Muscular Atrophy and Congenital Myopathy compared to usual care

Secondary Objective(s):
2) To determine the efficacy of personalized PRT on muscle strength of elbow flexors in children and adolescents combined with DMT compared to DMT alone as usual care, in patients with SMA.
To determine the efficacy of personalized PRT on muscle strength of elbow flexors in children and adolescents with CM compared to usual care.
3) To determine the efficacy of personalized PRT on muscle strength of elbow flexors in children and adolescents with a *red muscle* compared to a *white muscle* profile.
4) To determine the clinical relevant effect of personalized PRT on muscle strength of elbow flexors in children and adolescents with Spinal Muscular Atrophy and Congenital Myopathy compared to usual care.

Study design

Multicenter randomized controlled double-blinded trial.

Intervention

14-week, 3 times weekly supervised progressive resistance training. The training program will be personalized with respect to training load and exercises, guided by individual treatment goals.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit, and group relatedness:
The training group (controlled period: week 3-16) and the control group (follow-up period: week 17-31) will both receive a progressive resistance training program of arm and shoulder muscles (30-45 minutes, 3 times a week,14 weeks) during this study. To reduce the burden of traveling, training sessions

will be performed at home or at their local physical therapy practice. All training sessions will be physically supervised and closely monitored, affording further tailoring of the training program when needed. Participants will visit UMCU three times, AMC or UMCU one time (with a second visit optional to reduce total burden), and will be visited once at home over a time period of 31 weeks. The three mandatory UMCU hospital visits (Spieren voor Spieren Inspanningslab) for functional and electrophysiological muscular evaluation will take 2-3 hours (note: standard care for these patients is one or two annual sessions of 2-3 hrs for multidisciplinary examination featuring similar assessmments of motor function, muscle strength and questionnaires). The mandatory single visit to AMC Hospital or UMCU hospital (Department of Radiology and Nuclear Medicine) for Magnetic Resonance metabolic and morphological muscular assessment will take 90 min. Patients will be screened for contra-indications before undergoing MR examination. A optional second visit after 14 weeks will inform on any muscular metabolic and morphological treatment response. All functional (strength), electrophysiological (EMG), morphological (MRI and metabolic (MRS) measurements are feasible and have negligible risks. They have been frequently used and are well tolerated in usual care and (ongoing) research performed in our Center with METC approval (METC-nr: 14-230/NL48715.041.14, 14-536/NL38048.041.14, 09-307). The risk of strength training is negligible. Spinal Musclar Atrophy and Congenital Myopathy have no increased risk of exercise-induced muscle damage and recent studies report no adverse events. Patients will be closely monitored and training intensity will be adapted when necessary. The criteria of the Nederlandse Vereniging voor Kindergeneeskunde (Dutch Association of Paediatrics) concerning research involving children will be strictly applied. Subjects may experience direct benefits from participating in this study in the form of a clinical relevant improvement in muscle function. Clinicians will gain more insight into the effects and working mechanism of personalized PRST, the importance of combinatory treatement and which individual muscle profiles may benefit most from PRST. This will help them to optimize and personalize training programs exercise for their patients and provide patients with a new treatment option to improve daily life activities, leisure activities, and sports participation. *

Contacts

Public
Universitair Medisch Centrum Utrecht

Lundlaan 6
Utrecht 3594CX
NL
Scientific

Universitair Medisch Centrum Utrecht

Lundlaan 6
Utrecht 3594CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

• Genetically confirmed diagnosis of SMA5q or CM27
• Age 10 to 30 years old.
• Ability to execute a biceps-curl with at least 1 kg

Exclusion criteria

• Insufficient understanding of the Dutch language.
• Inability to meet study visits
• Experimental treatment that may alter muscle function (eg myostatin inhibitors)
• Considering adjusting the dose of medication during the study that might affect the motor unit function (e.g. pyridostigmine, salbutamol)
• Risk factors for exercise testing registered by a Dutch version of the preparticipation Questionnaire (American College of Sports Medicine and American Heart Association). Possible risk factors will be discussed with a medical exercise physiologist and neurologist before a subject can be included.
• Medical disorders i.e. comorbidities or being under examination, that prohibit progressive resistance training or could influence the intervention

outcome.
• Surgery affecting training ability < 3-6 months prior to the start of the program, depending on the type of surgical intervention (e.g. scoliosis correction).
• Pregnancy or current wish to become pregnant.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-11-2024
Enrollment:	46
Type:	Actual

Ethics review

Approved WMO Date:	26-09-2024
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-01-2025
Application type:	Amendment
Review commission:	METC NedMec

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	NL85860.041.24