**Whole-body vibration training as a therapy to improve mobility, muscle and bone health in children and adolescents with Duchenne Muscular Dystrophy**

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**STUDY PROTOCOL**

**Study design**

This study will have a single intervention group, comparing baseline (T0), a control period of 20 weeks (T1), and post-treatment outcomes (T2). All participants will undergo 20 weeks of WBVT between T1 and T2. This study design effectively allows for the participants to act as their own controls with an initial 20 week observation period. Due to the small numbers of children with DMD, a randomised control trial design is not feasible. A cross-over design is also inappropriate, as the effects of WBVT are likely to be long-standing (weeks to months).

Any patients unable to travel to Auckland for the full assessments, who would like to participate, will be included as a control group with assessments at T0 and T2.

**Treatment**

During the lead in period of 20 weeks (T0 – T1) patients will continue their usual activity levels and standard care. This control period will allow for better assessment of efficacy. WBVT will then be performed on the Galileo Basic vibration plate (Novotec Medical, Pforzheim, Germany). Each session will consist of three 3-minute bouts of training, interspersed with a 3-minute rest. Sessions will be performed four times a week, over a 20- week period (T1 – T2). Participants will start with sessions of three 1-minute bouts at 12 Hz, and both intensity and duration will be gradually increased according to the response of each individual. However, by the end of week 4, all participants should be training at the prescribed protocol of 3 sets of 3 minutes at 20 Hz and 1 mm amplitude, 4 times a week. Training intensity will be maintained at 20 Hz for the remainder of the intervention. This training protocol is a well validated clinical paradigm used in previous published literature1.

Participants will stand barefoot on the plate. An adjustable metal frame will initially be used with all participants until they build up confidence and are able to safely support themselves during the vibration training. For participants with poor balance, the frame will be maintained at all times to safely regain balance when necessary. Training sessions will be performed at home. An experienced exercise physiologist and/or a specialist physiotherapist from the research team will supervise the participants performing training at home or school once a week, in order to monitor progress and provide feedback/support. Parents/caregivers will provide ongoing supervision of home sessions. Participants will be asked to maintain a training diary to monitor compliance. Data recorded will include the date, intensity and duration of training, as well as any comments regarding adverse events, tiredness, or pain.

We will provide participants with a Fitbit to monitor activity levels and resting heart rate.

**Participants**

Patients with DMD will be identified from the New Zealand Neuromuscular Disease Registry database, Neuromuscular clinic, and Neurology Clinical Network. Participants will be aged 8- 18 years. The Registry indicates that there are 55 – 65 patients with DMD in New Zealand.

We estimate that 15 - 20 patients in Auckland fulfil inclusion criteria and a further 20 patients throughout the country. We aim to recruit 20 participants to undergo WBVT training (see power calculations below for justification of participant population number). Participants will continue their standard therapy (physiotherapy, splints, steroid medication etc.) throughout the trial. Based on our previous experience recruiting for the cerebral palsy trial, parents and participants demonstrated great interest in WBVT and the recruitment rate was high.

Only participants with mild to moderate mobility will be recruited, i.e. those who are able to: i) stand on the vibration platform for the duration of treatment sessions, and ii) undergo the clinical and functional assessments necessary to evaluate treatment outcomes. Mobility would be GMFCS Level I to Level IV, and patients would need to be able to complete a 6MWT without the use of a wheelchair (but may use a walking aid).

**Exclusion criteria include:**

1) A bone fracture within 8 weeks of enrolment;

2) Acute thrombosis, tendinitis, nephrolithiasis, discopathy or arthritis;

3) History of another illness or findings on physical examination, which in the opinion of the investigators would prevent the patient from completing the study;

4) Use for ≥30 days of medication that might interfere with study results and assessments within 3 months of enrolment (e.g. anabolic agents);

5) Patients who have started bisphosphonate treatment within 12 months of the intervention.

6) Vertebral compression of Genant grade 3 or greater;

7) Vitamin D deficiency at screening (serum 25-hydroxyvitamin D concentrations <50nmol/l); note that if a potential participant is deficient and management of low vitamin D is possible to bring levels above 50 nmol/l, the individual can become eligible.

**Treatment safety**

Previous studies have demonstrated the safety of WBVT in children with DMD for 4 2, 8 3, and 12 weeks 4. These studies indicate that WBVT is well tolerated in patients with DMD, with no evidence of muscle function deterioration or sustained changes in creatine kinase levels. Subjects will be closely monitored and participants and their families will be asked to record and report any adverse events that may be associated with the WBVT, including tiredness or pain. Individual training sessions will stop if the participant displays fatigue.

WBVT will be discontinued in any participant who:

1) Experiences excessive or persistent pain/aching;

2) Displays rising creatine kinase (CK) levels (an indicator of muscle inflammation and/or damage), greater than 100% above baseline, plus an ongoing increase in CK of >20% after three more training days OR

3) A rise in CK of >40,000IU/L after starting the WBVT; or

4) Experiences bone fractures or any illness that would preclude training.

The CK parameters have been adopted from previous studies 3. CK levels are known to vary significantly in affected individuals, throughout the day and at 6 week intervals. The mechanism for this remains unexplained, but there is no indication that CK levels correlate with clinical severity. In patients who continued WBVT, CK level returned to baseline without modification of the intervention, and with no deleterious change in objective measures.

**Power calculation**

There are two major outcomes we wish to power for in this study. The first is improved function and mobility. Based on our data1 from adolescents with mild to moderate cerebral palsy the standard deviation was 41metres for the 6 minute walk test. A clinically relevant improvement is considered to be more than 35 to 40 metres. This translated into greater independence and better quality of life scores. Using a paired repeated measures design, a standard deviation of 49metres 1, an alpha of 0.05 and a power of 0.8 we would need 15 subjects to see a difference of 39 metres after whole body vibration. The second outcome is improved bone health and a reduced risk of steroid induced osteoporosis. Again from data obtained for our previous studies using WBVT and using the same alpha and power above with a standard deviation of 0.03 cm/m2 we could detect a difference in bone mineral density of 0.14 cm/ m2 with a sample size of 15 1. We plan to recruit 20 subjects assuming a 20-25% drop out, although drop out form our cerebral palsy studies has been generally <10%.

**Assessments**

All participants will undergo 3 clinical assessments (at baseline (T0), at the start of the intervention (T1) and after the 20 week intervention (T2)) at the Maurice and Agnes Paykel Clinical Research Unit (Liggins Institute, University of Auckland). The assessments are internationally recognised, and have been performed in a similarly disabled population with cerebral palsy 1. The assessments are short, not difficult to achieve, and are often enjoyable! All assessments can be done within half a day. The functional assessments are complete within 1 hour, DEXA scan within 30 minutes, and pQCT within an hour. Each assessment will be tailored to the ability of the patient. We have listed several varied assessments in order to assess for functional outcomes. A standardised Excel Datasheet will be used to record data.

**Assessments:**

1) Serum creatine kinase will be measured at baseline, and monthly during the lead-in period. During the intervention, creatine kinase will be measured once weekly for the first 4 weeks, and then monthly for the remainder of the study. During the intervention period, the creatine kinase will be measured on the morning after the last vibration treatment for the week.

2) Height will be measured using a Harpenden stadiometer.

3) Blood pressure and pulse rate will be measured in a sitting position at rest prior to the start of functional tests and immediately after completion. We will use a standard mercury sphygmomanometer (Dinamap ProCare 100, GE Healthcare, Freiburg, Germany), with an appropriately-sized cuff on the non-dominant arm.

4) Body composition and skeletal data will be obtained using whole-body dual-energy X-ray absorptiometry (DXA, Lunar Prodigy 2000, General Electric, Madison, WI, USA) to determine lean mass, fat free mass, fat mass, body mass, bone mineral density, and bone mineral content.

5) Blood tests will be performed for the assessment of serum 25-hydroxyvitamin D and markers of bone and muscle turnover, such as serum bone-specific alkaline phosphatise (BALP), serum osteocalcin, type I collagen degradation, P1NP, PTH, calcium, phosphate, ESR, ALT, and TNF-α. These will be done at T0, T1 and T2, ie. The majority of these tests are done on only 3 blood-letting occasions.

6) Physical function will be assessed by the 6-minute walk test 19. In brief, participants will be asked to walk as fast as possible for exactly 6 minutes, with the total distance covered and the time taken to reach individual milestones recorded. Participant will be able to stop and rest if necessary, and then continue walking until the 6 minutes are completed. Participants may use a walking aid to complete the test (but not a wheelchair).

7) Muscle function will be assessed using the Leonardo Mechanography Ground Reaction Force Plate (Novotec Medical, Pforzheim, Germany), including:

i) the chair rising test – performed with a specially-designed seat (Novotec Medical) placed on the plate, with participants standing up and sitting down three times as fast as possible;

ii) single two-leg jump – jumping as high as possible using both legs and landing on the forefoot;

iii) balance test – standing still on the plate for 10 seconds.

8) Peripheral quantitative computed tomography (pQCT) (Stratec Medizintechnick Gmbh, Pforzheim, Germany) will be used to obtain cross-sectional measurements of tibial bone mass and calf muscle. Measurements will be obtained at 4% and 38% sites along the tibia.

9) Quality of life will be assessed using the Child Health Questionnaire 5 at T0 and T2.

10) A Fitbit will be provided to the participants in order to assess overall mobility (through the pedometer) and resting heart rate. 1 week of typical activity will be analysed at T0, T1 and T2.

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