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Feasibility, safety, and efficacy of 12-week side-to-side vibration therapy in children and adolescents with congenital myopathy in New Zealand

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ABSTRACT

This pilot study explored the feasibility and effectiveness of vibration therapy (VT) on muscle and bone health, motor performance, and respiratory function in patients with congenital myopathy (CM). Eleven participants with CM (11.5 ± 2.8 years) underwent 12 weeks of side-alternating VT at 20 Hz for nine minutes per session, four days a week. VT was preceded by a 12-week control period. Assessments included dual-energy X-ray absorptiometry scans, 6-minute walk and 10-meter run tests, muscle function and motor performance assessment, dynamometry, and pulmonary function. VT was well-tolerated, with occasional mild itchiness reported. The median compliance level with VT treatment was 75%. 12 weeks of VT improved the total score of motor function performance by 2.4 units (p=0.006) and velocity rise maximum of the chair rising test by 0.11 m/s (p=0.029). VT was shown to be feasible, safe, and associated with improving motor function performance. Our findings support further exploration of VT's potential health benefits to patients with CM in larger studies involving a longer intervention period.

1. Introduction

Congenital myopathies are a group of rare inherited muscle conditions and clinically manifest with non-progressive or slowly-progressive muscle weakness and hypotonia [1,2]. Recent estimates of CM prevalence worldwide are 1.37-5:100000 depending on the country and population age group (i.e. paediatric patients, adults) [2–4]. In New Zealand, crude prevalence of CM was reported to be 1.41:100000 [5].

The severity of the clinical symptoms and the location of affected muscles depend on CM type and the underlying genetic cause [6–8]. Muscle weakness commonly presents in axial and proximal limbs, affecting motor development and walking ability, and also reducing overall exercise endurance [2,9,10]. Limb muscle weakness and reduced mobility are associated with altered bone development, increasing the risk of osteopenia [10,11] and bone fragility [12,13]. Another common clinical manifestation in patients with CM is the weakness of respiratory muscles, which can lead to abnormal pulmonary function, recurrent respiratory infections, and both acute and chronic respiratory insufficiency [2,10,14,15].

According to the "Consensus Statement on Standard of Care for Congenital Myopathies" published by a committee of medical professionals in 2012 [10], the principles of optimal care for CM patients should include pulmonary care, orthopaedic management, and neuropsychological evaluation and management. Orthopaedic management aims to maintain and maximize muscle strength and function, bone health, and promote physical activity and exercise endurance [10]. The Consensus Statement also highlighted that exercise rehabilitation should be an integral part of daily care for patients with CM [10]. However, very little information exits on available therapies and their application.

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Vibration therapy (VT) is a promising exercise rehabilitation modality that has been suggested to be explored in patients with CM [10,16]. VT is a weight-bearing exercise modality performed on a vibration platform that produces impulses, leading to stimulation of the muscle spindle and initiating muscle cyclic elongation and contraction [17]. VT could be applied in different modes: synchronous and side-alternating. Vibration signals in the synchronous mode transfer to both feet synchronously, so both legs extend and stretch simultaneously. The side-alternating VT provokes legs activation alternatively, so that one leg goes up and the other one goes down (similar to see-saw movements). This leads to a rotary component in the lumbar spine and, therefore, reduces vibration transmission to the trunk and head [18]. Side-alternating VT is the most commonly used VT mode in children [19], possibly due to better tolerability to vibration impulses given less head vibration [20].

To date, VT has been shown to improve muscle and bone health in patients with a range of musculoskeletal conditions, including Duchenne muscular dystrophy (DMD) [21,22], cerebral palsy (CP) [23–25], spinal muscular atrophy [22], postmenopausal osteoporosis [26], fibromyalgia [27], and others [28]. VT has been reported to increase muscle strength and power [23–25], areal bone mineral density (aBMD) [23,25,26], improve balance [28,29], and muscle tone [24]. Studies have also demonstrated an increase in walking endurance [23,28], motor function [24,25,27], and health-related quality of life in these groups [23,27]. In addition, VT has been reported as a useful rehabilitation tool for patients with respiratory conditions, demonstrating improvements in pulmonary function [30], aerobic capacity [30–33], and quality of life [30,33] in patients with chronic obstructive pulmonary disease.

VT is well tolerated with few reported side effects, which are nonetheless minor and transient such as temporary skin redness and itchiness of the calf and ankle area, which subside quickly after VT completion [18]. Studies examining the potential impacts of VT on muscle damage both in laboratory settings (i.e. creatine kinase and lactate dehydrogenase) and clinically (i.e. muscle pain and fatigue) reported no deleterious changes and/or termination of VT training due to increased muscle damage [21,22,34,35].

Therefore, VT may be a potentially beneficial therapy for patients with CM improving muscle health and function and, consequently, increase walking endurance and modify the course of osteopenia. VT could also improve pulmonary function in these patients.

To the best of our knowledge, no published studies have explored the effectiveness of VT on walking ability, bone health, and pulmonary function in patients with CM. The present study sought to investigate the feasibility, safety, and efficacy of short-term side- alternating VT on muscle and bone health, gross motor function, as well as respiratory function in children and adolescents with CM.

2. Materials and methods

2.1. Study population

Eligible participants were children and adolescents with CM aged 4 to 16 years, who were able to stand on a vibration plate and understand the instructions for the study's assessments and VT protocol. Participants were recruited from Children's Health Paediatric Neuromuscular Clinics at the Starship Children's Hospital in Auckland (New Zealand), and the New Zealand Neuromuscular Disease Registry. The exclusion criteria included: a fracture within 8 weeks prior to enrolment; use of medications that could interfere with study outcomes (e.g. bisphosphonates, systemic steroids, and growth hormone); acute thrombosis; tendinitis; nephrolithiasis; discopathy; arthritis; history of an illness or findings on physical examination that might prevent a person from completing the study; vertebral compression of Genant grade 3 or greater; and cognitive impairment that might affect the ability to participate in testing procedures.

2.2. Study design

This study was a non-randomized, prospective interventional study with a single intervention group, where all participants acted as their own controls (Fig. 1). This design was adopted due to the very limited pool of potential participants in New Zealand [5]. Participants underwent three clinical assessments: at baseline (T0), 12 weeks after the control (lead-in) period (T1), and after completing 12 weeks of VT (intervention period; T2).

2.2.1. Control period

During the 12-week control period (T0–T1), participants were asked to continue with their usual activity levels and standard care. The control period served as a baseline for comparison to the results of the subsequent intervention period, which would determine the efficacy of VT.

2.2.2. Intervention period

During the intervention period (T1–T2) participants underwent 12 weeks of home-based side-alternating VT. VT was performed on a Galileo Basic vibration plate (Novotec Medical, Pforzheim, Germany) at the target frequency of 20 Hz and amplitude of 2 mm, for 9 min a day (in 3 min bouts of VT, alternating with 3 min breaks between them), four times a week. Participants started with three 1 min bouts at the frequency of 12 Hz, gradually increasing both VT frequency and duration over the first 4 weeks until the target frequency and duration were achieved. During VT, participants stood barefoot on the plate with feet placed at an equal distance from the centre of the board (i.e. "0" mark), straight back and knees slightly bent (Fig. 2). For participants with poor balance, an adjustable metal frame was used for safety purposes. At the end of the second assessment visit, all participants and their caregivers had a 20 min instructions session covering vibration platform operation and correct posture/position on the plate. In addition, researchers discussed the supervision of VT sessions with the parent(s)/caregiver(s). Subsequently, participants had three 1-min training sessions under the supervision of the researchers, with postural correction if needed. Families were then supplied with a vibration plate for the 12 weeks of home-based VT. Throughout the VT period, a member of the research team provided support/feedback to participants to monitor progress and correct technique: once a week in the first four weeks, then once every two weeks for the remaining 8 weeks. Participants and their families were also asked to maintain a diary to monitor compliance with study protocols, and record any comments regarding potential adverse events, tiredness, or pain. Full compliance (100%) was defined as completion of all 48 sessions at the required intensity and duration.

2.3. Assessments

Clinical assessments were carried out at the Maurice and Agnes Paykel Clinical Research Unit at the Liggins Institute, University of Auckland, Auckland. All assessments were performed by the same researchers and in the same order at all clinical visits.

2.3.1. Anthropometry and body composition

Height was measured to the nearest 1 mm using a wall-mounted Harpenden stadiometer (Holtain Ltd., Crymych, UK) three times, with the average result recorded. Weight was measured to

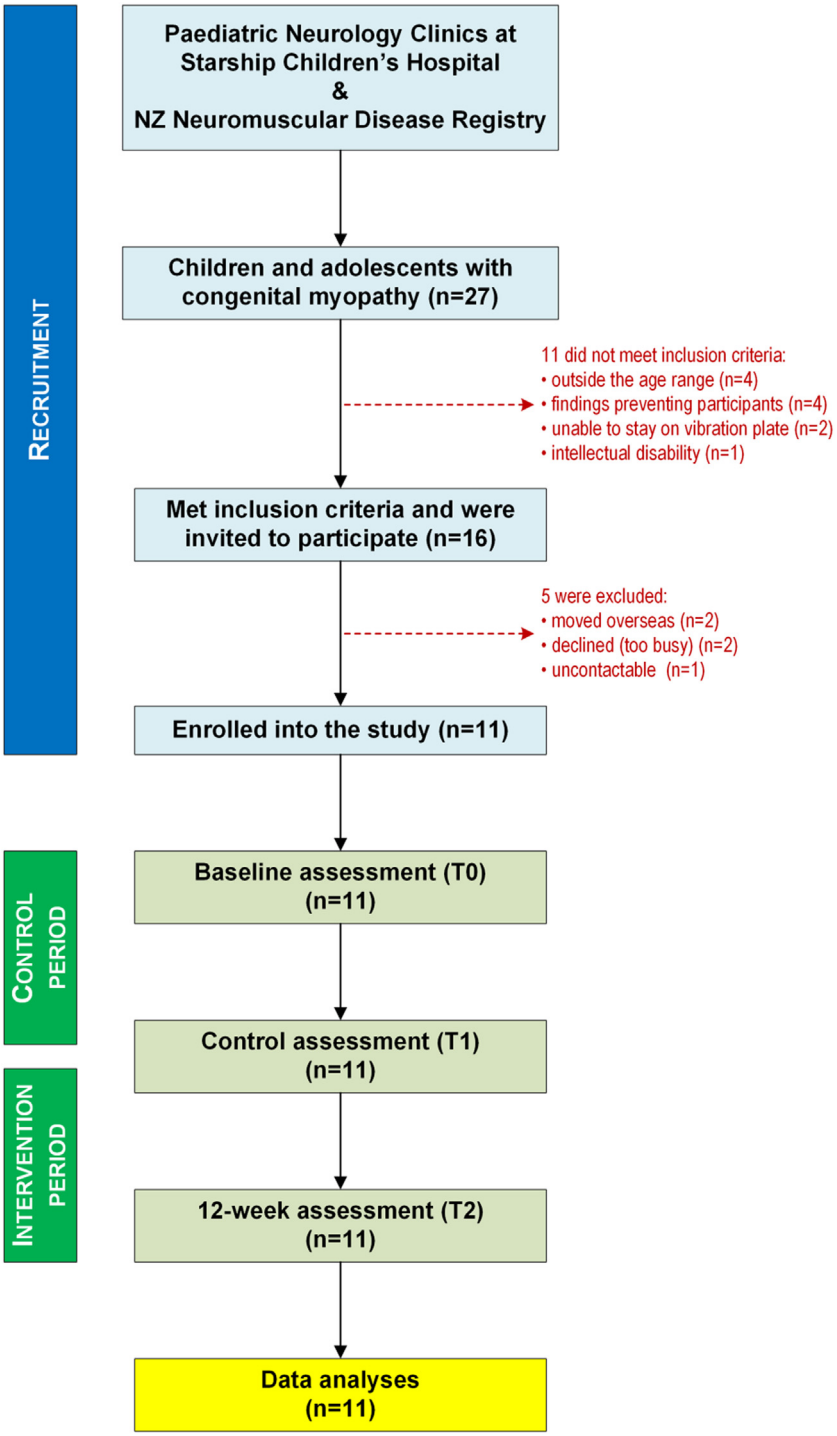

Fig. 1. Diagram showing the recruitment and flow of participants with congenital myopathy throughout the study.

the nearest 0.1 kg on a calibrated electronic scale (Wedderburn WM206, Auckland, NZ) without shoes and while wearing light clothing. Body mass index (BMI) was subsequently calculated (as kg/m^2), with sex- and age-specific z-scores derived for height, weight, and BMI according to the World Health Organization reference charts [36]. Body composition was assessed using whole-body dual-energy X-ray absorptiometry (DXA) scans (Lunar Prodigy 200, GE, Madison, WI, USA) [37]. Key parameters of interest were BMD and bone mineral content (BMC) of total body and lumbar spine images (L1–L4 in the anteroposterior direction).

2.3.2. Functional tests

Physical function was assessed with the 6-minute walk (6MWT) and 10-meter run test (10MRT). For 6MWT, participants were asked to walk as fast as possible for 6 min following standard guidelines [38,39]. The test was performed with shoes on, and participants used their walking aid or orthotics if required. The total distance covered was recorded to the nearest 0.5 m, along with the time taken to reach individual milestones (50 m).

For the 10MRT, participants were instructed to run as fast as possible, and the time to cover 6 meters was recorded, with two meters given for both acceleration and deceleration. The test was

Fig. 2. Participant position on the Galileo Basic vibration plate during vibration therapy session.

performed while barefoot, three times, with the average recorded for analysis. Those participants, who were unable to walk/run independently did not perform the test.

The Leonardo^{TM} Mechanography Ground Reaction Force Plate (Novotec Medical, Pforzheim, Germany) was used to measure dynamic muscle strength. Participants' tasks included a single two-legged jump (S2LJ) with freely moving arms, the chair rising test (CRT), and a balance test on both legs [40,41]. Each test was performed three times, with the best result recorded for analysis (i.e., the highest jump, the shortest time, and the smallest elliptical area, respectively).

A hand-held dynamometer (HHD) (MicroFET2, Hoggan Scientific, USA) was used to measure isometric muscle strength using a "make" technique. Participants were instructed to gradually "push as hard as possible" over three seconds against the HHD held rigidly by the examiner perpendicular to the child's limb [42]. Measurements have been done on the dominant side (determined according to the hand dominance) in five lower limb muscle groups: ankle dorsiflexion, hip extension, knee flexion, hip flexion, and knee extension. Each muscle group was tested three times, with the average result recorded for analysis.

2.3.3. Motor function performance

Participants also completed the motor function measurement assessment (MFM-32), which evaluates the severity of motor disability in patients with CM [43]. It consists of 32 items, which are divided into 3 dimensions: D1 – standing and transfers (13 items; e.g., standing from sitting position, sitting up from supine position, standing on one leg with/without support), D2 – axial and proximal limb motor function (12 items; e.g., turning over from supine position to prone, rising head while in the supine position, maintaining sitting position on the chair with the head and trunk remain in midline position), and D3 – distal limb motor function (7 items; e.g., foot dorsiflexion from plantar flexion position, tearing a sheet of paper folded in 4) [43]. The total maximum score is 96 points [43].

2.3.4. Respiratory function (spirometry)

Respiratory function was assessed using a CareFusion MicroLab MK8 spirometer (Care Fusion; Chatham, Kent, UK). Before each measurement, participants rested for 10 min. Measures included forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and their ratio FEV1/FVC [44]. We also recorded information on the ventilatory pattern (normal, obstructive, or restrictive) derived from the spirometer's automatically generated conclusion. At least three technically appropriate measurements were performed, with the best result taken for statistical analysis.

2.4. Statistical analyses

Study outcomes were assessed using linear mixed models. Models included visit as a fixed factor, and family ID to account for the non-independence of siblings. In addition, models followed a repeated measures design based on Participant ID to account for the repeated (and non-independent) measurements made on the same individual over time. In addition, outcomes expressed in units strongly affected by the participant's growth over time (e.g. parameters expressed in g or kg) also included age at assessment as a covariate, to account for the potential effects of the participant's growth over the study period. Data on study outcomes at each visit are reported as the raw means and respective 95% confidence intervals (CI). Outcome differences between visits are provided as the least squares means (i.e., adjusted means) and respective 95% CI, more specifically, after the control period (i.e., T1 - T0) and after VT (T2 - T1).

The distance covered by our participants during the 6MWT at baseline was compared to a reference population of non-CM children with typical development using two-sample t-tests [45]. In addition, we compared our participants' baseline mean values for the S2LJ Esslinger Fitness Index [41] and respiratory function to age- and sex-matched reference values [44] (target mean of 100%) using one-sample t-tests.

Data were analysed using SAS v9.4 (SAS Institute, Cary, NC, USA), SPSS v25 (IBM Corp, Armonk, NY, USA), and Minitab v19 (Pennsylvania State University, State College, Pennsylvania, USA). All statistical tests were two-sided, with statistical significance maintained at $p<0.05$ without adjustment for multiple comparisons as per Rothman (1990) [46].

2.5. Ethics approval

Ethics approval was granted by the Central Health and Disability Ethics Committee (16/CEN/179). This study followed the principles of the World Medical Association's Declaration of Helsinki, adhering to all appropriate guidelines and regulations for medical research [47]. Written informed consent was obtained from legal parents/guardians, as well as written consent/assent from all participants, as appropriate for their age. The trial was registered at the Australian New Zealand Clinical Trials Registry (ANZCTR: 12616001471471).

3. Results

3.1. Participants

Sixteen children and adolescents with CM out of twenty-seven registered in New Zealand Neuromuscular Disease Registry and Paediatric Neurology Clinic database (Starship Children's Hospital, Auckland) met eligibility criteria and were invited to participate. From those, 11 individuals agreed to participate (Fig. 1). Diagnoses

Table 1
Characteristics of study participants.

n		11
Age (years)		11.3 [9.2, 13.0]
	Males	4 (36%)
	Females	7 (64%)
Ethnicity	New Zealand European	7 (64%)
	Māori	3 (27%)
	Pacific	1 (9%)
Mobility level *	Ambulant	9 (82%)
	Partially ambulant	1 (9%)
	Non-ambulant	1 (9%)
CM-related gene (type of inheritance)	RYR1 (AD)	2 (18%)
	ACTA1 (AD de novo)	1 (9%)
	TPM2 (AD)	3 (27%)
	NEB (AR)	1 (9%)
	TTN (AR)	2 (18%)
	COL12A1 (AD de novo)	1 (9%)
	Unknown**	1 (9%)

AD, Autosomal dominant; AR, Autosomal recessive.
Age data are median [quartile 1, quartile 3]; other data are n (%).
* Ambulant – does not need walking assistance; partially ambulant – wheelchair required for long-distance; non-ambulant – unable to walk independently.
** Clinical diagnosis only. Neuromuscular gene panel negative.

included RYR1-, ACTA1-, TPM2-, NEB-, and TTN-related myopathies (Table 1). One patient recently diagnosed with COL12A1-related myopathy was included because histological findings were those of congenital myopathy, rather than congenital muscular dystrophy. One patient did not have a genetic diagnosis. Please note that a different number of subjects completed the individual assessments, and the respective *n* is provided in the tables with the results.

3.2. Anthropometry and body composition

Anthropometric and body composition outcomes are presented in Table 2. There were no observed changes in anthropometry (i.e., height, weight, and BMI z-scores). Leg BMC increased over the control period [+15.9 g (95% CI 6.3, 25.5); p=0.002] compared to baseline but was unchanged after VT (Table 2). TBLH aBMD decreased after the intervention compared to the control period [-0.014g/cm^2 (95%CI -0.028, 0.000); p=0.049] (Supplementary Fig. 1E). There were no other observed changes in BMC or aBMD after the control or VT periods (Table 2).

3.3. Functional assessments

The study participants performed poorly in the functional tests. At baseline, excluding non-ambulant child, they covered a mean distance of 485 m (SD=106) in the 6MWT (Supplementary Fig. 1A) in comparison to 664 m (SD=65) for a population of non-CM children with normal development [-179 m (95% CI -255, -103); p=0.0005] [45]. The mean value of the S2LJ Esslinger Fitness Index, which compares the jump power per kg of body weight to a predicted age/sex-matched reference and measured in percentage, was 47.2% (95% CI 34.8, 60.0) and markedly lower than the predicted 100% (p<0.0001) [41].

There were no observed changes in functional tests after the control period compared to baseline (Table 3). However, the intervention was associated with an improvement in the velocity rise maximum (VRM) in the chair rising test [+0.11 m/s (95% CI 0.01, 0.21); p=0.029] (Supplementary Fig. 1C), but a decrease in knee flexion strength [-0.8 kg (95% CI -1.4, -0.2); p=0.008] (Supplementary Fig. 1F) compared to the control period (Table 3). Other functional parameters appeared to be unchanged throughout the study, including the 10MRT (Supplementary Fig. 1B) (Table 3). Further, clinically, no participants reported any changes in muscle strength and/or muscle soreness.

3.4. Motor function performance

Motor function parameters were unchanged after the control period (Table 4). However, in comparison to the control period, 12 weeks of VT led to improvements in the total MFM-32 score [+2.4 (95% CI 0.7, 4.0); p=0.006] (Supplementary Fig. 1D), and in dimensions D1 [+1.5 (95% CI 0.6, 2.5); p=0.002] and D3 [+0.5 (95% CI 0.0, 0.9; p=0.042] that reflect standing/transferring skills and distal limb motor function, respectively (Table 4).

3.5. Respiratory function (spirometry)

The majority of participants (n=7; 64 %) had impaired pulmonary function at baseline. Among them, five (45.5 %) showed mild to moderate restriction, and two (18.2%) had severe restriction. At baseline, participants had relatively low FVC and FEV1 that were 72.1% (95% CI 54.2, 90.0; p=0.011) and 77.2% (95% CI 59.2, 95.3; p=0.038) of predicted age/sex-matched values, respectively (Table 5). Their forced expiratory ratio was within the normal range [94.3 (95% CI 90.3, 98.3)], although slightly lower than the reference value (p=0.011). There were no changes in respiratory function results after the control and intervention period (Table 5).

3.6. Vibration therapy

Home-based VT was well accepted by participants and their parents/caregivers. Using a home-based device was called a positive aspect of the therapy as participants were not limited by such barriers as a lack of time or the necessity of transportation to and from the treatment venue. The frequency (4 days/a week) and duration of a single VT session (9 min/session) were reported as acceptable and feasible for participants and their families. There was no 'ideal' time for the VT sessions identified by the families as time varied depending on their other commitments. There were no reported operating issues with the vibration plate. All but one participant were able to keep balance on the vibration plate and perform VT with freely moving arms. A non-ambulant participant used a stability bar for support during VT sessions.

3.7. Compliance and adverse effects

Compliance with the VT protocol was high (median=75%). The main reasons reported for missing VT sessions were lack of time or being away. Overall, VT was well-tolerated and no severe adverse events were reported. Two participants mentioned lower back pain during the first two sessions, which was resolved after posture correction by the researchers in a monitored session. Five participants reported occasional mild itchiness in the calf and ankle areas noted during the first three weeks of VT, which resolve quickly (within a minute) after cessation of the VT session.

4. Discussion

Our study showed that VT is a feasible, acceptable, and likely safe form of therapy for children and adolescents with CM. Participants did not report increased fatigue and muscle soreness, and initial reports of lower back pain in two participants were easily addressed with correction of posture during VT sessions. The ease of use of a vibration plate makes it suitable for home-based use by children and adolescents with CM.

We implemented a VT protocol with a gradual increase of vibration frequency and sessions' duration from 12 Hz of 3 min

Table 2
Anthropometric and body composition outcomes.

Parameters		T0	T1	T2	T1-T0	p-value	T2-T1	p-value
Anthropometry	Height z-score	0.64 (0.03, 1.26)	0.65 (0.03, 1.26)	0.62 (0.00, 1.23)	0.00 (-0.07, 0.08)	0.90	0.03 (-0.11, 0.05)	0.45
	Weight z-score	0.18 (-0.76, 1.12)	0.12 (-0.82, 1.06)	0.04 (-0.91, 0.98)	0.06 (-0.16, 0.28)	0.93	0.08 (-0.13, 0.30)	0.81
	BMI z-score	-0.16 (-1.25, 0.94)	-0.25 (-1.34, 0.85)	-0.33 (-1.43, 0.76)	-0.09 (-0.31, 0.12)	0.39	-0.09 (-0.30, 0.13)	0.43
aBMD	TBLH (g/cm^2)* (n=11)	0.696 (0.617, 0.774)	0.709 (0.630, 0.787)	0.711 (0.632, 0.789)	0.001 (-0.013, 0.015)	0.92	-0.014 (-0.028, 0.000)	**0.049**
	TBLH (z-score) (n=11)	-0.99 (-1.73, -0.25)	-0.95 (-1.70, -0.21)	-1.01 (-1.75, -0.26)	0.0 (-0.1, 0.2)	0.61	-0.1 (-0.2, 0.1)	0.47
	Legs (g/cm^2)* (n=11)	0.783 (0.682, 0.884)	0.788 (0.687, 0.890)	0.817 (0.715, 0.918)	-0.010 (-0.030, 0.009)	0.29	0.008 (-0.012, 0.028)	0.41
	Spine (g/cm^2)* (n=10)	0.815 (0.698, 0.933)	0.821 (0.704, 0.939)	0.824 (0.707, 0.942)	-0.013 (-0.035, 0.009)	0.23	-0.021 (-0.043, 0.001)	0.06
	Spine (z-score) (n=10)	-0.43 (-1.40, 0.54)	-0.47 (-1.43, 0.50)	-0.58 (-1.54, 0.39)	0.0 (-0.3, 0.2)	0.74	-0.1 (-0.3, 0.4)	0.30
BMC	TBLH (g)* (n=11)	997 (792, 1202)	1033 (828, 1239)	1049 (843, 1254)	6 (-26, 39)	0.70	-23 (-59, 16)	0.20
	Leg (g)* (n=11)	452 (344, 560)	468 (360, 576)	475 (367, 583)	5 (-11, 22)	0.52	-6 (-25, 13)	0.50
	Spine (g)* (n=10)	32.4 (25.5, 39.3)	33.4 (26.5, 40.3)	34.7 (27.8, 41.6)	-0.2 (-1.6, 1.1)	0.71	-0.1 (-1.5, 1.2)	0.86
Lean mass	TBLH (kg)*	20.4 (16.6, 24.1)	21.1 (17.3, 24.8)	21.6 (17.8, 25.4)	0.3 (-1.0, 1.5)	0.66	0.0 (-1.3, 1.3)	>0.99
	Leg (kg)*	7.1 (5.6, 8.7)	7.2 (5.6, 8.8)	7.3 (5.8, 8.9)	-0.15 (-0.47, 0.16)	0.33	-0.15 (-0.47, 0.17)	0.35

BMI, body mass index; aBMD, areal bone mineral density; TBLH, total body less head; BMC, bone mineral content.
T0 – baseline assessments, T1 – assessments after the control period, T2 – assessments after 12 weeks of vibration therapy. T0, T1, T2 values are the means and respective 95% confidence intervals (CI); T1-T0 and T2-T1 are the least squares means (i.e., adjusted means) for the differences between the two assessments (and respective 95% CI) derived from linear mixed models based on repeated measures; * indicates the parameters whose models also included the participant's age at assessment as a covariate. p-values for statistically significant differences (at $p<0.05$) between time-points are shown in bold.

Table 3
Functional outcomes.

Parameters		T0	T1	T2	T1-T0	p-value	T2-T1	p-value
Physical activity								
6 MWT distance (m)* (n=10)		441 (332, 550)	458 (349, 567)	467 (358, 576)	10 (-14, 34)	0.41	1 (-23, 25)	0.96
10MRT time (s)* (n=10)		2.13 (1.81, 2.44)	2.09 (1.77, 2.40)	2.02 (1.70, 2.33)	-0.03 (-0.18, 0.12)	0.72	-0.05 (-0.20, 0.10)	0.46
Leonardo mechanography								
CRT (n=9)	Total time (s)	5.4 (3.7, 7.0)	5.7 (4.1, 7.4)	5.9 (4.3, 7.6)	0.4 (-0.8, 1.4)	0.52	0.2 (-0.9, 1.3)	0.71
	Velocity rise max (m/s)	0.72 (0.51, 0.92)	0.71 (0.50, 0.92)	0.82 (0.62, 1.03)	0.01 (-0.11, 0.09)	0.89	**0.11 (0.01, 0.21)**	**0.029**
	Power max (kW)*	0.32 (0.18, 0.47)	0.35 (0.20, 0.49)	0.38 (0.23, 0.52)	0.01 (-0.05, 0.08)	0.66	0.02 (-0.05, 0.09)	0.55
S2LJ (n=9)	Jump height (m)*	0.16 (0.10, 0.21)	0.15 (0.10, 0.21)	0.17 (0.12, 0.22)	-0.01 (-0.02, 0.01)	0.50	0.01 (-0.01, 0.03)	0.15
	Power max (kW)*	0.76 (0.46, 1.05)	0.74 (0.45, 1.04)	0.78 (0.48, 1.08)	-0.04 (-0.13, 0.05)	0.38	0.00 (-0.09, 0.09)	0.96
Balance (n=10)	Standard ellipse area (cm^2)	0.83 (0.11, 1.56)	0.66 (-0.07, 1.38)	0.91 (0.15, 1.68)	-0.18 (-1.05, 0.70)	0.69	0.32 (-0.59, 1.23)	0.48
Dynamometry								
Ankle dorsiflexion (kg)* (n=10)		3.7 (3.2, 4.3)	3.4 (2.8, 3.9)	3.4 (2.9, 3.9)	-0.4 (-0.8, 0.1)	0.09	-0.0 (-0.5, 0.4)	0.93
Hip extension (kg) * (n=10)		5.8 (4.8, 6.8)	6.2 (5.2, 7.2)	5.9 (4.9, 6.9)	0.4 (-0.5, 1.3)	0.39	-0.4 (-1.3, 0.5)	0.40
Hip flexion (kg)* (n=11)		7.8 (6.0, 9.7)	8.3 (6.4, 10.1)	7.8 (6.0, 9.7)	0.3 (-0.9, 1.6)	0.60	-0.6 (-1.9, 0.7)	0.34
Knee extension (kg)* (n=11)		8.3 (6.5, 10.0)	8.6 (6.9, 10.4)	8.2 (6.4, 9.9)	0.2 (-0.8, 1.2)	0.66	-0.6 (-1.6, 0.4)	0.21
Knee flexion (kg)* (n=11)		4.8 (4.0, 5.7)	4.9 (4.0, 5.7)	4.2 (3.3, 5.0)	-0.01 (-0.6, 0.6)	0.98	-0.8 (-1.4, -0.2)	**0.008**

6MWT, six minute walk test; 10MRT, ten meters run test; CRT, chair rising test; S2LJ, single two-leg jump p-values for statistically significant differences (at $p<0.05$) between time-points are shown in bold.T0 – baseline assessments, T1 – assessments after the control period, T2 – assessments after 12 weeks of vibration therapy. T0, T1, T2 values are the means and respective 95% confidence intervals (CI); T1-T0 and T2-T1 are the least squares means (i.e., adjusted means) for the differences between the two assessments (and respective 95% CI) derived from linear mixed models based on repeated measures; * indicates the parameters whose models also included the participant's age at assessment as a covariate.

Table 4
Motor function outcomes.

Parameters	T0	T1	T2	T1-T0	p-value	T2-T1	p-value
D1	30.2 (23.2, 37.1)	30.5 (23.5, 37.4)	32.0 (25.0, 39.0)	0.3 (-0.7, 1.2)	0.56	**1.5 (0.6, 2.5)**	**0.002**
D2	33.3 (29.9, 36.6)	33.2 (29.8, 36.5)	33.5 (30.2, 36.9)	-0.1 (-0.8, 0.6)	0.80	0.4 (-0.3, 1.1)	0.31
D3	18.9 (17.0, 20.8)	19.2 (17.3, 21.1)	19.6 (17.7, 21.5)	0.3 (-0.2, 0.7)	0.22	**0.5 (0.0, 0.9)**	**0.042**
Total score	82.4 (70.7, 94.0)	82.8 (71.2, 94.4)	85.2 (73.6, 96.8)	0.5 (-1.2, 2.1)	0.58	**2.4 (0.7, 4.0)**	**0.006**

D1, standing position and transfers; D2, axial and proximal motor function; D3, distal motor function.
T0 – baseline assessments, T1 – assessments after the control period, T2 – assessments after 12 weeks of vibration therapy. T0, T1, T2 values are the means and respective 95% confidence intervals (CI); T1-T0 and T2-T1 are the least squares means (i.e., adjusted means) for the differences between the two assessments (and respective 95% CI) derived from linear mixed models based on repeated measures.
p-values for statistically significant differences (at $p<0.05$) between time-points are shown in bold.

Table 5
Spirometry results.

Parameters	T0	T1	T2	T1-T0	p-value	T2-T1	p-value
FVC (l)	2.18 (1.77, 2.58)	2.17 (1.76, 2.57)	2.28 (1.88, 2.69)	-0.01 (-0.20, 0.19)	0.94	0.12 (-0.08, 0.31)	0.24
FVC %	76.0 (63.1, 88.9)	73.6 (60.7, 86.6)	76.0 (63.1, 88.9)	-2.4 (-8.4, 3.6)	0.43	2.4 (-3.6, 8.4)	0.43
FEV1 (l)	2.04 (1.67, 2.40)	1.96 (1.60, 2.32)	2.06 (1.70, 2.42)	-0.07 (-0.29, 0.14)	0.48	0.10 (-0.11, 0.31)	0.35
FEV1 %	81.5 (68, 94.9)	75.8 (62.3, 89.3)	77.8 (64.3, 91.3)	-5.6 (-11.4, 0.14)	0.06	2.0 (-3.8, 7.8)	0.49
FEV1/FVC	94.6 (90.9, 98.2)	90.8 (87.1, 94.4)	90.5 (86.8, 94.1)	-3.8 (-8.0, 0.3)	0.07	-0.3 (-4.5, 3.8)	0.88

FVC, forced vital capacity; FEV1, forced expiratory volume in one second; FEV1/FVC, forced expiratory ratio.
T0 – baseline assessments, T1 – assessments after the control period, T2 – assessments after 12 weeks of vibration therapy. T0, T1, T2 values are the means and respective 95% confidence intervals (CI); T1-T0 and T2-T1 are the least squares means (i.e., adjusted means) for the differences between the two assessments (and respective 95% CI) derived from linear mixed models based on repeated measures.
p-values for statistically significant differences (at $p<0.05$) between time-points are shown in bold.

per session targeting the frequency of 20Hz and session length of 9 min from the end of week 4 till the end of the intervention period. To date, there is no standardized VT protocol for use in children and adolescents with musculoskeletal disorders. However, a similar protocol has been successfully utilized in previous studies in children and adolescents with CP [23,48] and a heterogeneous group of musculoskeletal disorders [28]. Given the present results, the described specifications for the VT protocol could be used as a basis for future research in patients with CM.

The benefits of 12 weeks of side-alternating VT were observed primarily in motor function performance. Several studies have reported a similar effect of VT on motor performance in children and adolescents with CP. Stark et al. (2010) found an improvement in gross motor performance in individuals with CP (n=78; 2–24 years) after 24 weeks of VT [25]. Ibrahim and colleagues also reported improvements in motor function after 12 weeks of VT in 15 children with CP (aged 8–12 years) [24]. One of the theories behind these changes is the impact of vibration stimuli on proprioception. It is suggested that VT stimulates the central nervous system via proprioceptive pathways, improving motor skills [49]. It is important to note that the reported improvement in motor function outcomes in our study could also reflect normal motor development considering the relatively brief observation (control) period. Therefore, our findings need to be confirmed in future studies.

The small and heterogeneous nature of the study cohort, particularly with respect to puberty makes the assessment of bone health and the impact of VT difficult. The lack of observed differences in bone markers expressed as z-scores (i.e., adjusted for age and sex, and to some extent pubertal status) indicates that 3 months of VT might not have been sufficient to improve bone health. This is not surprising given that previous data suggest at least 5 months of VT would be required to yield improvements in aBMD and BMC [21,23,25,50]. Gusso et al. (2016) have shown improvement in TBLH, lumbar spine, and lower limbs aBMD and BMC in 40 children and young adults with CP after 20 weeks of VT [23]. Similar results were observed by Stark and colleagues (2010) in total body aBMD and BMC following 24 weeks of VT in 78 participants with CP aged 2–24 years [25]. In contrast, Söderpalm et al. (2013) reported no changes in densitometry parameters after 12 weeks of VT in 6 patients with DMD aged 5.7–12.5 years [21]. We recommend that future studies should involve a longer VT intervention period, as 12 weeks of VT treatment in this study was likely insufficient to lead to detectable changes in bone health.

Dynamometry tests indicated a decrease in knee flexor's strength. However, this was an isolated finding that should be interpreted with caution, particularly since there were no associated clinical signs (e.g., increase in muscle weakness and/or fatigue, or a decrease in walking endurance). Also, there were no observed changes in strength in the other muscles tested, while the velocity rise maximum (CRT) increased after the intervention period. Thus, it is unclear whether the observed decline in knee flexor's strength was due to VT or simply an isolated spurious finding.

The present study did not detect any effects of VT on mobility or muscle endurance (assessed by 6MWT and 10MRT), or respiratory function. Our findings corroborate previous studies in children with DMD that did not show any benefits of VT on muscle function or strength [21,22,34]. Both conditions, CM and DMD, are morphologically characterized by structural defects in skeletal muscles. CM is caused by abnormalities in the structural proteins of muscle cells and components that support efficient excitation-contraction coupling [6,51]. DMD is caused by an unstable dystrophin protein in the sarcolemma that leads to degeneration of muscle fibers [52]. Nonetheless, VT did have a positive effect on muscle function and strength in patients with CP

[23–25,29] and other musculoskeletal disorders [28] whose muscle weakness is caused by different mechanisms.

The limitations of our study included the absence of a control group and a heterogeneous group of participants, both due to the low number of patients with CM registered in New Zealand. Also, our intervention period of 12 weeks of VT was probably too short and, likely insufficient to yield detectable improvements in bone health. Further, our small study population means our study had reduced statistical power, which would have affected to some extent our ability to detect statistically significant changes in most clinical outcomes. Lastly, the many study health outcomes assessed mean that, except for the consistent improvements in motor function, observed isolated VT effects on other outcomes need to be interpreted with caution. Nonetheless, these findings support the need for larger studies to ascertain whether our observations would be corroborated by larger studies, in particular multicentre clinical trials that could overcome the small pool of potential participants at a given locality. In addition it should be noted that our primary aim was to determine the feasibility and safety of VT for children and adolescents with CM.

5. Conclusions

12 weeks of home-based VT were safe, feasible, and associated with improvements in motor function in children and adolescents with CM. Our findings support further exploration of VT effectiveness on bone and muscle health of patients with CM in larger studies with a longer intervention period.

Authors' contributions

CFM, LCP, GOG, PLH, and SG designed the study and protocol submission. AA, SG, GOG, LCP recruited. AA and SG carried out clinical assessments. AA managed the study database, and extracted data for analyses. JGBD analysed the data. AA drafted the manuscript with input from SG and JGBD. CFM, GOG, and PLH critically revised the manuscript. All authors have approved the final submitted version.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2022.07.398.

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