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Efficacy of Low-magnitude High-frequency Vibration (LMHFV) on Musculoskeletal Health of Subjects on Wheelchair: A Study Protocol for A Single-blinded Randomized Controlled Study

Simon Kwoon-Ho Chow [1, 2], Chung Yan Ho [1], Hiu Wun Wong[1], Yu Ning Chim[1], Ronald Man Yeung Wong [1], Wing Hoi Cheung [1, 2]

Author Affiliations

[1] Department of Orthopaedics and Traumatology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China.

[2] The CUHK-ACC Space Medicine Centre on Health Maintenance of Musculoskeletal System, The Chinese University of Hong Kong Shenzhen Research Institute, Shenzhen, PR China.

Correspondence to:

Wing Hoi Cheung, PhD, Department of Orthopaedics and Traumatology, 5/F, Clinical Sciences Building, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China.

E-mail: louischeung@cuhk.edu.hk; Telephone: (852) 3505-1559; Fax: (852) 3505-4618

ABSTRACT

Introduction

Low-magnitude high-frequency vibration (LMHFV) is a non-invasive biophysical intervention providing whole-body mechanical stimulation shown to benefit muscle strength, postural control, balancing ability, new bone formation, spinal bone mineral density (BMD), and blood circulation. Current LMHFV treatment requires elderlies to stand upright on the platform 20min/day, making it difficult for those with a poor musculoskeletal ability who cannot stand for long periods. Therefore, the vibration platform is modified to treat disabled patients at sitting position, which efficacy of LMHFV on this group of elderlies will be verified. It is hypothesized that the new design of LMHFV is beneficial to wheelchair users in terms of vertebral BMD, muscle health and musculoskeletal functions.

Methods and analysis

This is a single-blinded randomized controlled trial that investigates the effect of LMHFV on vertebral BMD, muscle health, balancing and functional ability in wheelchair users.

Healthy elderlies aged 65 years or above, with walking difficulties and using a wheelchair are eligible. Recruited subjects will be randomized to either LMHFV or control group. The primary outcome is to access lumbar spine BMD by dual-energy X-ray absorptiometry (DXA) that is clinically recommended for osteoporosis diagnosis. All primary and secondary outcome assessments will be performed at baseline and 6 months post-treatment. Two-way repeated measures ANOVA will be used to compare measured outcomes between two groups at different time points.

Ethics and dissemination

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong (Ref. no 2019.087-T). Results will be disseminated through peer-reviewed publications, conferences, and workshops.

Trial registration number

ClinicalTrials.gov, NCT04180267.

Keywords

Osteoporosis, Vibration Therapy, Wheelchair users, Vertebral BMD, LMHFV

Strengths and limitations of this study

- This is the first study that investigates the efficacy of LMHFV on wheelchair users, hence data generated will be with high clinical translation values.
- This trial cannot be double-blinded since blinding subjects for the LMHFV treatment is not feasible.
- The vibration signals can be easily felt and placebo is rare in vibration studies.

INTRODUCTION

Ageing is an emerging socio-economic problem in Hong Kong. The ageing population at 65 or above increased continuously from 0.46 million (8.2%) to 1.27 million (17.9%) from 1988 to 2018 [1]. The prevalence of osteoporosis also increases due to the escalating ageing population[2]. Osteoporosis is an age-induced disorder with progressive loss of bone that leads to deterioration of bone microarchitecture and hence low BMD. It increases the risk of fragility fracture known to be associated with increased morbidity and mortality[3].

Elderly people with disability or mobility impairments due to trauma, chronic illnesses or over-weight may avoid walking and rely on wheelchairs for most daily activities. Many studies showed that wheelchair users had greater bone loss compared to walkers[4 5]. Physical activity is one of the recommended approaches for preventing osteoporosis. However, some elderly people may be restricted from exercise training because they are not physically fit to perform the intensive exercise[6], leading to a vicious cycle of musculoskeletal deterioration.

Low-magnitude high-frequency vibration (LMHFV) is a promising intervention proposed as an alternative to physical exercise[7] for treating osteoporosis. It is a non-invasive biophysical intervention that provides systemic vertical vibrations at 20 - 90Hz at amplitude of less than 1.0g (g = gravitational acceleration)[8]. Previous studies demonstrated that LMHFV treatment could enhance muscle strength[9], postural control[10], balancing ability[6 11 12], new bone formation[13-15], spinal BMD[6], and blood circulation[6].

There were some studies reporting the effect of whole-body vibration treatment on wheelchair users with spinal cord injury. They showed that whole-body vibration treatment could increase upper limb performance during propulsion of the wheelchairs in terms of average speed and time

of displacement and blow flow to paralyzed muscles in the lower limbs[16-18]. However, there is a lack of evidence for the effect of LMHFV on elderly people with poor walking and standing ability (such as subjects on wheelchair), which is a missing gap of our knowledge.

In this study, we hypothesize that LMHFV would enhance the musculoskeletal health of the elderly people with walking difficulties and relying on wheelchairs for daily mobility, in terms of vertebral bone quality and muscle performance. The objective is to investigate the effects of LMHFV on vertebral BMD, muscle performance and balancing ability in disabled elderly subjects. The vibration platform will be modified to suit the disabled patients for treatment at sitting position. The results of this study would broaden the indications of vibration platform to benefit more people in the community, which have a good potential of translation.

METHODS AND ANALYSIS

Study design

This is a single-blinded randomized controlled trial to study the effects of LMHV on vertebral BMD and muscle performance of disabled elderly. This is a two-year study, in which the recruited wheelchair users will receive a 6-month LMHFV treatment.

Study participants

Subjects will be recruited from the specialist outpatient clinic or orthopaedic wards of the Prince of Wales Hospital (PWH) of the Chinese University of Hong Kong, or community centers or elderly homes. Subjects will be recruited based on the inclusion and exclusion criteria. All

recruited subjects will be requested by an investigator to give a written consent and will perform the following assessments at the PWH.

Inclusion criteria

Inclusion criteria are listed as follows:

1. Subjects of both genders aged ≥ 65 years.
2. Subjects with walking difficulties, especially those who usually walk indoor but use wheelchairs outdoor.
3. Subjects with good general health conditions.

Exclusion criteria

Exclusion criteria are as follows:

1. Subjects cannot stand and walk independently.
2. Subjects who had vibration treatment before.
3. Subjects with malignancy.
4. Subjects with acute fractures or severe osteoarthritis[19].
5. Subjects with cardiovascular concern such as with pace-maker in-situ.
6. Subjects with chronic inflammatory conditions known to affect muscle metabolism such as rheumatoid arthritis.
7. Subjects with high frequency of physical activities, such as subjects who participated in regular exercise five times a week or more.

Randomization and grouping

After baseline assessment, eligible subjects will be randomized by sealed-envelope drawing of computer-generated random numbers. The random number list is kept strictly confidential and the researchers will not have access to the list. They will be randomized into either one of two groups: LMHFV or control group.

Assessments

Two groups of subjects will be subjected to the same assessments: [1] demographic data collection; [2] BMD measurement at the spine (primary outcome) and hip; [3] handgrip strength; [4] quadriceps strength; [5] balancing ability test, [6] quality of life (QoL); and [6] adverse event reporting, if any. The compliance of the subjects in LMHFV group will be recorded in a SD card in the machine; meanwhile the subjects will be given a calendar to self-record the usage for counter-checking. A flow diagram of the whole trial is shown in Figure 1.

Interventions

After baseline visit, regular phone reminders will be used to remind subjects to complete their LMHFV interventions and about the date of their end-point assessments. Contacts will be provided for any queries during the study.

LMHFV is a non-invasive biophysical intervention providing whole-body vibration signals for mechanical stimulation. Subjects are required to sit upright on the vibration platform (V-Health Limited, Hong Kong) providing a frequency 35 Hz, 0.3× gravitational acceleration at peak-to-peak displacement of less than 0.1 mm for 20 min/day. Treatment will be given for at least 3 days/week. In this study, the design of vibration platforms is modified for wheelchair users. A chair and a supporting footrest are fixed on the platform (Figure 2). Subjects are instructed to sit on the chair and rest their feet on the footrest for 20 min/day. The research staff will instruct safety precautions

and operative procedures. Each patient in the control group will remain in their habitual life style without vibration treatment.

Blinding

Investigators, outcome assessors and the statistician will be blinded to the grouping allocation that is performed by one independent staff and kept confidential from team members. Outcome assessments will be performed by a central technician at the Bone Quality and Health Centre of the Chinese University of Hong Kong, who has obtained International Society for Clinical Densitometry (ISCD) certificate and is independent from this project. All subjects will be reminded not to disclose their grouping to the assessors. However, blinding the subjects for the LMHFV treatment is not feasible because the vibration signals can be easily felt and placebo is rare in vibration studies[6 11].

Primary outcome measures

All primary and secondary outcome assessments for the two groups will be performed at baseline and 6 months post-treatment.

The primary outcome of this study is vertebral BMD. BMD will be assessed by standard DXA (Delphi W, Hologic, Waltham, MA, USA) which is a gold standard assessment for osteoporosis recommended by World Health Organization (WHO). Spine and hip are the two standard sites for the diagnosis of osteoporosis and both will be measured. The only ethical concern is the additional DXA assessments, which emits a low-dose radiation at 10 microSv, roughly equivalent to 1 day exposure to natural background radiation. In our institute, the short-term precision error of areal BMD (aBMD) by DXA was 2.07% at the femoral neck and 1.35% [20] at the lumbar spine.

Secondary outcome measures

Secondary outcomes include muscle strength assessment, balancing ability and quality of life (QoL).

Handgrip strength and quadriceps strength will be assessed. Handgrip strength will be measured by dynamometer (5030JI, JAMAR, USA) on dominant hand of each subject. Participants will be instructed to hold the device with the arm at right angle and elbow to the side of the body. The maximum effort will be taken from 3 trials[21]. Quadriceps strength will be measured by instructing the subjects to perform an active extension of the knee joint at a sitting position with both feet free from the ground, and the hip and knee joint flexed at 90º. The peak forces of the knee extension will be measured by a dynamometer attached at the malleoli level and repeated thrice in each lower limb with the maximum force taken for analysis[6].

To assess the balancing ability, modified functional reach test [22] and postural stability test will be performed. Modified functional reach test is a simple test for fall risk assessment[23]. It measures the maximal distance that the subject can reach when the subjects sits on a bench with their hip, knees, and ankles positioned at 90° of flexion, with feet positioned flat on the floor. A level yardstick will be mounted on the wall at the height of each subject's acromion of the non-paretic side, while sitting on bench with no back or arm rests. Subjects are required to lean as far as possible in each direction without rotating or touching the wall. The furthest position of the fifth finger will be marked on the yardstick. If the subject cannot raise the paretic arm, the distance covered by the acromion during leaning will be used[19]. Postural stability test measures subjects' ability to maintain their center of balance. Center of pressure (COP) is the average point at which the body concentrates. COP can be tested by Biodex Balance System (Biodex Medical Systems, Inc, NY, USA). Subjects are required to sit on the platform without support from feet and keep

arms folded across chest. Thighs need to be kept parallel, with 75% of their length supported on the platform[24].

To assess the health-related quality of life, validated Chinese version of the 36-item Short-Form Health Survey (SF-36) will be used for quantitative evaluation of the subjects' physical and mental component summary. Subjects with higher scores indicate a general better quality of life[6 25].

Recruitment Strategy

Subjects will be recruited for this RCT through two approaches: 1) Promotional and educational talks at community centres; 2) Collaboration with social workers from each collaborating community centre.

Before recruitment, they will be informed of the potential benefits and risks of the interventions in this study. They will then be required to fill out an informed consent and can withdraw from this study without any condition.

Sample size calculation

Vertebral BMD is used as the primary outcome in this study. Our previous bedrest study[26] showed that vibration could reduce the loss of bone mineral density at various skeletal sites by 5-10%. The total sample size is estimated to be 70 subjects using two-way repeated measures ANOVA with power at 0.8 and alpha of 0.05. With consideration of around 15% dropout, the sample size is increased to n=80.

Data analysis

Two-way repeated measures ANOVA will be used for comparing the measured outcomes between two groups at different time points. SPSS version 25.0 (IBM, NY, USA) will be used to perform analysis and significance level is set at $p<0.05$.

Data monitoring

All investigators will be responsible for record keeping. Only principle and co-investigators, authorized research personnel and Ethical Committee can access to the personal data during and after the study. All data collection will be performed with strict adherence to the professional standards of confidentiality. Any personal information, including subjects' name, address, phone number etc., will be removed from all records. Important documents will be retained for at least 3 years after the completion of the study for final report and inspection.

Data Statement

Data and resources will be shared with other eligible investigators through academically established means. The protocol and datasets used or analysed in this study will be available from the corresponding author upon reasonable request. Researchers who provide a methodologically sound proposal may access data to achieve aims in the approved proposal.

Patient and public involvement

Patients and the public were not involved in the design or planning of the study. Members of the public are involved in the recruitment of participants or conduct of the study. We will report test results to participants in plain language after their end-point assessments are completed. Results will be available to the public and patients in the forms of educational talks and booklets or flyers and published in open access peer-reviewed journals.

Ethics and dissemination

The study protocol has been approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong (Ref. no 2019.087-T). Trial results will be published in peer-reviewed journals and disseminated at relevant conferences and to the public via educational talks and booklets or flyers.

DISCUSSION

To our knowledge, this is the first study to investigate the efficacy of low-magnitude high-frequency vibration therapy (LMHFV) on wheelchair users. As the worldwide ageing population escalates, the number of people with mobility impairment or disability would also increase[27]. These people would inevitably be relying on wheelchair to assist their daily living[28]. Wheelchair-bound elderlies usually have limited physical activity and is therefore associated to lower BMD[29] and ability to control body position, and thus have an increased risk of fall and osteoporotic fractures. A study from Grant Medical Center in the United States investigated 30 wheelchair-bound subjects who fell from wheelchair over a 5 years period[30]. The report showed that elderlies who were older than 65 years of age with higher fall risk were associated with lack of physical activity and poor nutrition, leading to a decrease in muscle mass and strength. As most osteoporotic fractures are caused by combination of poor balance, falls, and deteriorating bone strength. Therefore, LMHFV is the proposed strategy to target musculoskeletal deterioration in wheelchair users for the prevention of more detrimental consequences.

LMHFV has previously been reported to have positive effects on reducing fall and fracture risks, enhancing muscle strength and improving balancing ability in healthy community-dwelling older

people[6 31]. Supported with this evidence, it is therefore hypothesized that LMHFV would provide positive effects on the musculoskeletal health and physical performance in terms of BMD, muscle strength, balancing ability on elderlies with disability or mobility impairments who rely on wheelchairs for locomotion.

Vibration is a good treatment modality that is easy to implement for physically challenged patients, like wheelchair users. However, there is a scarce of literature reporting its effect on this group of patients who are most desperately in need of the treatment. There have been a few reports on the application of vibration treatment on wheelchair users with spinal cord injury (SCI). Menéndez's study reported in 2016 investigated the acute effect of whole-body vibration[18]. Ten patients with SCI were recruited and treated with various treatment schemes including the whole-body vibration (WBV). Patients were instructed to sit on wheelchairs with their feet rested on the vibration platform (Galileo Home, Galileo, Novotec, Germany, 10 Hz, 5 mm peak-to-peak). Their results have shown an enhancement to the mean blood velocity (MBV) and peak blood velocity (PBV) by approximately 25% at 7 minutes after a 1-minute vibration treatment. A separate study in 2016, also by Menéndez's group, investigated the long-term combined treatment effect of WBV and electromyostimulatin (ES) in SCI patients. Seventeen subjects with SCI were randomized into treatment group and control group for 12 weeks. Patients in treatment group received 30 sections of 10-minute WBV and ES stimulation over a 12-week period[17]. The treatment group was reported to show increased resting arterial diameter, increased blood flow, and increased muscle thickness at the gastrocnemius after 12 weeks of treatment. Although these studies employed a side-alternating vibration (instead of vertical-oscillating vibration) only to the lower limbs, these results suggested that mechanical stimulation in the form of vibration could provide benefits to blood flow that is associated with better performance-related outcomes in paralyzed skeletal muscles.

Therefore, suggesting that the proposed LMHFV treatment, providing a vertical oscillating stimulation (Figure 1B) to the whole-body would be beneficial to the target group of patients.

Findings of the current clinical trial would generate valuable data that is of high clinical translation values for wider application of vibration therapy in the community; and to generate clinical evidence that is not restricted to the healthy and mobile older people, but also to the group of patients with mobility impairments and high risk of further musculoskeletal function deterioration.

TRIAL STATUS

This trial is in process of planning subject recruitment.

ACKNOWLEDGEMENTS

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AUTHOR CONTRIBUTIONS

All the authors designed the study and composed the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong (Ref. no 2019.087-T) and conformed to the Declaration of Helsinki. Results will be disseminated through peer-reviewed publications, conferences and workshops.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare no conflict of interest.

ABBREVIATIONS

Low-magnitude high-frequency vibration (LMHFV)
Bone mineral density (BMD)
Areal BMD (aBMD)
X-ray absorptiometry (DXA)
Quality of life (QoL)
International Society for Clinical Densitometry (ISCD)
World Health Organization (WHO)
Center of pressure (COP)
36-item Short-Form Health Survey (SF-36)
Spinal cord injury (SCI)
Whole-body vibration (WBV)
Mean blood velocity (MBV)
Peak blood velocity (PBV)
Electromyostimulatin (ES)

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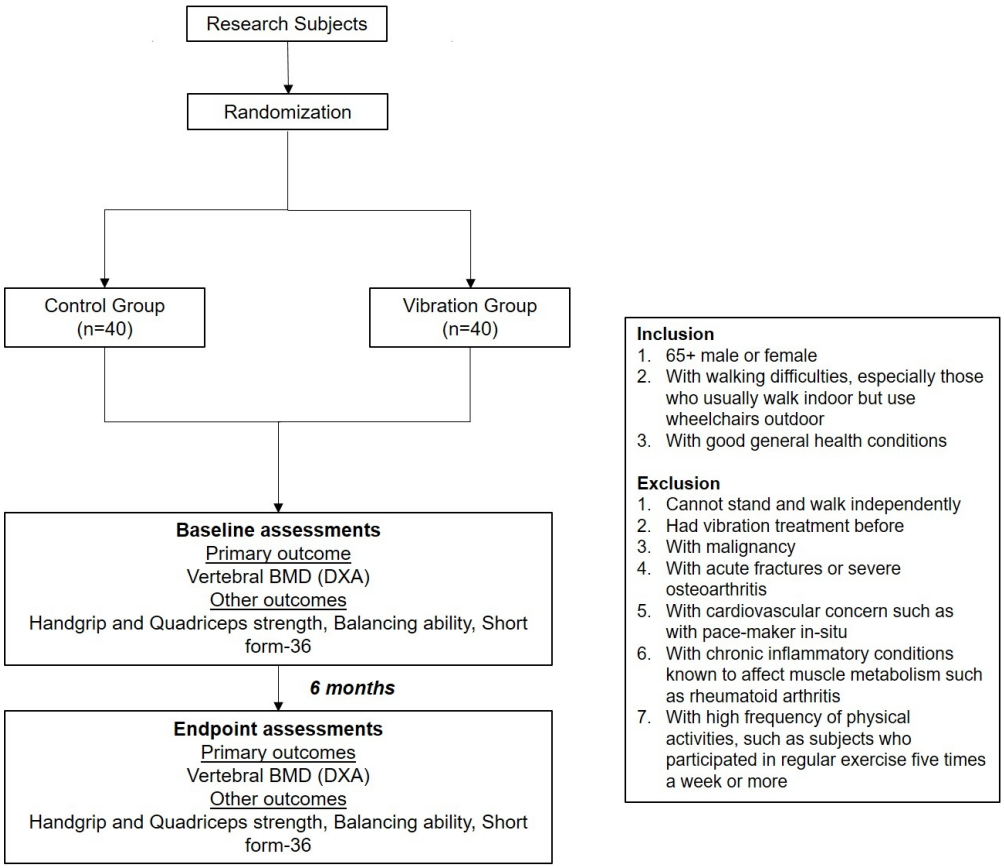
FIGURE LEGEND

Figure 1 Flow diagram showing the grouping and assessments in this study.

Figure 2 A vertical-oscillating vibration platform modified to provide a seating place for the research subject to receive the 20 min/day treatment. This representative vibration platform is installed in a community centre situated in a public housing estate with 6692 units/families in the Shatin district of Hong Kong.

Word count: 2862



Flow diagram showing the grouping and assessments in this study.

109x96mm (300 x 300 DPI)

A vertical-oscillating vibration platform modified to provide a seating place for the research subject to receive the 20 min/day treatment. This representative vibration platform is installed in a community centre situated in a public housing estate with 6692 units/families in the Shatin district of Hong Kong.

48x67mm (300 x 300 DPI)

低幅高頻振動治療
對使用輪椅，行動不便的的老年人在骨骼肌肉健康上的影響的研究
Efficacy of Low-magnitude High-frequency Vibration (LMHFV) on musculoskeletal health of subjects on wheelchair, a randomized controlled study

參加者同意書
Consent Form

我在此聲明：
I declare that:

1. 本人已閱讀及明白這份參與研究同意書，並且已經獲得提問的權利。我已經被知會我可能遇到的風險和得益。我所提出的問題已得到滿意的解答。
   I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. I have been told about the risks and benefits and I have had my questions answered to my satisfaction.
2. 我明白我的參與完全出於自願並且可以在任何時候退出，而無需任何理由。我的決定不會影響我所受到的醫療服務和法律權利。如果我決定退出這項研究，我同意之前收集到的資料可繼續被使用。
   I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. If I decide to withdraw from this study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.
3. 我明白機構審查委員會、倫理委員會或監察機構的成員可能會查閱我的醫療紀錄，我同意授權有關人員查閱我的記錄。
   I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. 我同意參與這項研究。
   I agree to take part in the above study.
5. 簽署這同意書並不表示我放棄任何權利。
   I do not waive any liability rights by signing this form.
6. 我的簽署表示我已得到這檔的副本。我會保留這副本直至我參與完結為止。
   My signature indicates that a copy of this form has been given to me and I will keep it until the end of my participation in the study.

_____	_____	_____
參與者的簽署 (Signature)	參與者姓名 (Name of participant)	簽署日期 (Date)
_____	_____	_____
研究者/代表簽署 (Signature of investigator or delegate)	研究者/代表姓名 (Name of investigator or delegate)	簽署日期 (Date)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	See this checklist
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	n/a
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	n/a

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4-5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-7; Figure 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	7

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-10

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	See comment

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed *(DMC is unlikely to have the opportunity to make a difference in this short term study where patient follow up is only 6 months and this study has minimal patient risk)*	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See uploaded document
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Efficacy of Low-magnitude High-frequency Vibration (LMHFV) on Musculoskeletal Health of Participants on Wheelchair: A Study Protocol for A Single-blinded Randomized Controlled Study

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Efficacy of Low-magnitude High-frequency Vibration (LMHFV) on Musculoskeletal Health of Participants on Wheelchair: A Study Protocol for A Single-blinded Randomized Controlled Study

Simon Kwoon-Ho Chow [1, 2], Chung Yan Ho [1], Hiu Wun Wong[1], Yu Ning Chim[1], Ronald Man Yeung Wong [1], Wing Hoi Cheung [1, 2]

Author Affiliations

[1] Department of Orthopaedics and Traumatology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China.

[2] The CUHK-ACC Space Medicine Centre on Health Maintenance of Musculoskeletal System, The Chinese University of Hong Kong Shenzhen Research Institute, Shenzhen, PR China.

Correspondence to:

Wing Hoi Cheung, PhD, Department of Orthopaedics and Traumatology, 5/F, Clinical Sciences Building, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China.

E-mail: louischeung@cuhk.edu.hk; Telephone: (852) 3505-1559; Fax: (852) 3505-4618

ABSTRACT

Background

Osteoporosis is an age-related disease with progressive loss of bone, leading to fragile bone. It is one of the major health issues in older adults and causes medical, social and economic impacts globally. Patients with osteoporosis have high risk of osteoporotic fractures. Low-magnitude high-frequency vibration (LMHFV) is a non-invasive biophysical intervention providing whole-body mechanical stimulation. Previous studies showed that LMHFV is beneficial to muscle strength, postural control, balancing ability, new bone formation, spinal bone mineral density (BMD), and blood circulation. During the LMHFV treatment, older adults need to stand upright on the platform for 20min/day. However, some physically weak elderlies with poor musculoskeletal ability cannot stand for a long period. Therefore, the design of vibration platform is modified for the disabled patients to treat at sitting position and the efficacy of LMHFV on this group of elderlies will be verified. It is hypothesized that new design of LMHFV is beneficial to wheelchair users in terms of vertebral BMD, muscle health and musculoskeletal functions.

Methods

This study is a single-blinded randomized controlled trial to investigate the effect of LMHFV on vertebral BMD, muscle health, balancing ability and functional ability in wheelchair users (mainly on wheelchair for outdoor activities).

Healthy elderlies aged 65 years or above, with walking difficulties and using wheelchair are eligible. Exclusion criteria are those: [1] cannot stand and walk independently, [2] have vibration treatment before, [3] with malignancy, [4] with acute fractures or severe osteoarthritis, [5] with

cardiovascular concern such as with pace-maker in-situ, [6] with chronic inflammatory conditions known to affect muscle metabolism such as rheumatoid arthritis, and [7] with high frequency of physical activities, such as participants who participated in regular exercise five times a week or more.

Recruited participants will be randomized to either LMHFV or control group. Participant assigned to LMHFV group will receive LMHFV (35Hz, 0.3g, 20min/day, at least 3 times/week) for 6 months. The primary outcome is BMD at the lumbar spine to be assessed by dual-energy X-ray absorptiometry (DXA) that is clinically recommended for the diagnosis of osteoporosis. All primary and secondary outcome assessments for all groups will be performed in the investigators' institute at baseline and 6 months post-treatment.

Discussion

This study aims to investigate the effects of LMHFV on wheelchair users. The findings of this study will help to confirm the efficacy of LMHFV on vertebral BMD, muscle health, balancing ability and functional outcomes in wheelchair using elderlies. LMHFV therapy is an intervention strategy that is easy to implement at the community healthcare level or individually at home that has previously been proven to reduce fall risk and muscle strength at the lower limb. The ultimate goal is to improve their bone and muscle quality of wheelchair users, as well as enhancing their quality of life.

Article summary

Strengths and limitations of this study

- This is the first study that investigates the efficacy of LMHFV on wheelchair users, hence data generated will be with high clinical translation values.

- This trial cannot be double-blinded since blinding subjects for the LMHFV treatment is not feasible.
- The vibration signals can be easily felt and placebo is rare in vibration studies.

Trial registration

ClinicalTrials.gov NCT04180267. Registered on Nov 26th, 2019.

Keywords

Osteoporosis, Vibration Therapy, Wheelchair users, Vertebral BMD, LMHFV

BACKGROUND

Ageing is an emerging socio-economic problem in Hong Kong. The ageing population at 65 or above increased continuously from 0.46 million (8.2%) to 1.27 million (17.9%) from 1988 to 2018 [1]. The prevalence of osteoporosis also increases due to the escalating ageing population [2]. Osteoporosis is an age-induced disorder with progressive loss of bone that leads to deterioration of bone microarchitecture and hence low BMD. It increases the risk of fragility fracture known to be associated with increased morbidity and mortality [3].

Older adults with disability or mobility impairments due to trauma, chronic illnesses or over-weight may avoid walking and rely on wheelchairs for most daily activities. Many studies showed that wheelchair users had greater bone loss compared to walkers [4 5]. Physical activity is one of the recommended approaches for preventing osteoporosis. However, some older adults may be restricted from exercise training because they are not physically fit to perform the intensive exercise [6], leading to a vicious cycle of musculoskeletal deterioration.

Low-magnitude high-frequency vibration (LMHFV) is a promising intervention proposed as an alternative to physical exercise [7] for treating osteoporosis. It is a non-invasive biophysical intervention that provides systemic vertical vibrations at 20 - 90Hz at amplitude of less than 1.0g (g = gravitational acceleration) [8]. Previous studies demonstrated that LMHFV treatment could enhance muscle strength[6], postural control [9], balancing ability [6 10 11], new bone formation [12-14], spinal BMD [6], and blood circulation [6].

There were some studies reporting the effect of whole-body vibration treatment on wheelchair users with spinal cord injury. They showed that whole-body vibration treatment could increase upper limb performance during propulsion of the wheelchairs in terms of average speed, time of displacement and blood flow to paralyzed muscles in the lower limbs [15-17]. However, there is a lack of evidence for the effect of LMHFV on older adults with poor walking and standing ability (such as non-paralyzed wheelchair users), which is a missing gap of our knowledge.

In this study, we hypothesize that LMHFV would enhance the musculoskeletal health of the older adults with walking difficulties and relying on wheelchairs for daily mobility, in terms of vertebral bone quality and muscle performance. The objective is to investigate the effects of LMHFV on vertebral BMD, muscle performance and balancing ability in disabled older participants. The vibration platform will be modified to suit the disabled patients for treatment at sitting position. The results of this study would broaden the indications of vibration platform to benefit more people in the community, which have a good potential of translation.

METHODS

Study design

This is a single-blinded randomized controlled trial to study the effects of LMHV on vertebral BMD and muscle performance of disabled older adults (Figure 1). This is a two-year study, in which the recruited wheelchair users will receive a 6-month LMHFV treatment. The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong (Ref. no 2019.087-T), with expected start date of January 1 of 2020 and end date of October 1 of 2021.

Study participants

Participants will be recruited from the specialist outpatient clinic or orthopaedic wards of the Prince of Wales Hospital (PWH) of the Chinese University of Hong Kong, or community centers or elderly homes. Participants will be recruited based on the inclusion and exclusion criteria. All recruited participants will be requested to give a written consent and will perform the following assessments at the PWH.

Inclusion criteria

Inclusion criteria are listed as follows:

1. Participants of both genders aged ≥ 65 years.
2. Participants with walking difficulties, especially those who usually walk indoor but use wheelchairs outdoor.
3. Participants with good general health conditions.

Exclusion criteria

Exclusion criteria are as follows:

1. Participants cannot stand and walk independently.

2. Participants who had vibration treatment before.
3. Participants with malignancy.
4. Participants with acute fractures or severe osteoarthritis [18].
5. Participants with cardiovascular concern such as with pace-maker in-situ.
6. Participants with chronic inflammatory conditions known to affect muscle metabolism such as rheumatoid arthritis.
7. Participants with high frequency of physical activities, such as participants who participated in regular exercise five times a week or more.

Randomization and Grouping

After eligibility screening, recruited participants will be randomized by sealed-envelope drawing of computer-generated random numbers. The random number list is kept strictly confidential and the researchers will not have access to the list. Research participants will be randomized into either one of two groups: LMHFV or control group.

Assessments

Two groups of participants will be subjected to the same assessments: [1] demographic data collection; [2] BMD measurement at the spine (primary outcome) and hip; [3] balancing ability test, [4] quality of life (QoL); and [5] adverse event reporting, if any. Compliance of the participants in LMHFV group will be recorded in an SD card in the treatment device while the participants will also be given a treatment calendar to self-record the usage for cross-validation. Adverse or fall events are recorded by a calendar provided to each participant who will be instructed to record the date and details of each event as previously reported [6].

Interventions

LMHFV is a non-invasive biophysical intervention providing whole-body vibration signals for mechanical stimulation. No known side effects are associated with this treatment except when a small risk of falling during the transfer of participants from the wheelchair to the treatment device. As the benefits discussed above including muscle strength[6], postural control [9], balancing ability [6 10 11], and blood circulation [6] may benefit wheelchair users' musculoskeletal health, risks of falling could be minimized with the help of the on-site researchers.

Participants are required to sit upright on the vibration platform (V-Health Limited, Hong Kong) providing a frequency 35 Hz, 0.3× gravitational acceleration at peak-to-peak displacement of less than 0.1 mm for 20 min/day. Treatment will be given for at least 3 days/week. In this study, the design of vibration platforms is modified for wheelchair users. A chair and a supporting footrest are fixed on the platform (Figure 2). Participants are instructed to sit on the chair and rest their feet on the footrest for 20 min/day. The research staff will instruct safety precautions and operative procedures. Each patient in the control group are instructed to maintain their habitual lifestyle without vibration treatment nor specific instructions given to take on additional physical exercise. Physical activities will be monitored via questionnaires.

Blinding

Investigators, outcome assessors and the statistician will be blinded to the grouping allocation that is performed by one independent staff and kept confidential from team members. Outcome assessments will be performed by a central technician at the Bone Quality and Health Centre of the Chinese University of Hong Kong, who has obtained International Society for Clinical Densitometry (ISCD) certificate and is independent from this project. All participants will be reminded not to disclose their grouping to the assessors. However, blinding the participants for

the LMHFV treatment is not feasible because the vibration signals can be easily felt and placebo is rare in vibration studies [6 10].

Primary outcome measures

All primary and secondary outcome assessments for the two groups will be performed at baseline and 6 months post-treatment.

The primary outcome of this study is vertebral BMD. BMD will be assessed by standard DXA (Delphi W, Hologic, Waltham, MA, USA) which is a gold standard assessment for osteoporosis recommended by World Health Organization (WHO). Spine and hip are the two standard sites for the diagnosis of osteoporosis and both will be measured. In our institute, the short-term precision error of areal BMD (aBMD) by DXA was 2.07% at the femoral neck and 1.35% [19] at the lumbar spine.

Secondary outcome measures

Secondary outcomes include muscle strength assessment, balancing ability and quality of life (QoL).

Handgrip strength and quadriceps strength will be assessed. Handgrip strength will be measured by dynamometer (5030JI, JAMAR, USA) on dominant hand of each participant. Participants will be instructed to hold the device with the arm at right angle and elbow to the side of the body. The maximum effort will be taken from 3 trials [20]. Quadriceps strength will be measured by instructing the participants to perform an active extension of the knee joint at a sitting position with both feet free from the ground, and the hip and knee joint flexed at 90º. The peak forces of the knee extension will be measured by a dynamometer attached at the malleoli level and repeated thrice in each lower limb with the maximum force taken for analysis[6].

To assess the balancing ability, modified functional reach test [21] and postural stability test will be performed. Modified functional reach test is a simple test for fall risk assessment [22]. It measures the maximal distance that the participant can reach when the participant sits on a bench with their hip, knees, and ankles positioned at 90° of flexion, with feet positioned flat on the floor. A level yardstick will be mounted on the wall at the height of each participant's acromion of the non-paretic side, while sitting on bench with no back or arm rests. Participants are required to lean as far as possible in each direction without rotating or touching the wall. The furthest position of the fifth finger will be marked on the yardstick. If the participant cannot raise the paretic arm, the distance covered by the acromion during leaning will be used [18]. Postural stability test measures participants' ability to maintain their center of balance. Center of pressure (COP) is the average point at which the body concentrates. COP can be tested by Biodex Balance System (Biodex Medical Systems, Inc, NY, USA). Participants are required to sit on the platform without support from feet and keep arms folded across chest. Thighs need to be kept parallel, with 75% of their length supported on the platform[23].

To assess the health-related quality of life, validated Chinese version of the 36-item Short-Form Health Survey (SF-36) will be used for quantitative evaluation of the participants' physical and mental component summary. Participants with higher scores indicate a general better quality of life[6 24].

Sample size calculation

Vertebral BMD is used as the primary outcome in this study. Our previous bedrest study [25] showed that vibration could reduce the loss of bone mineral density at various skeletal sites by 5-10%. The total sample size is estimated to be 80 participants using two-way repeated measures

ANOVA with power at 0.8 and alpha of 0.05. With consideration of around 15% dropout, the sample size is increased to n=80.

Data Analysis

Data in this study will be analysed according to the intention-to-treat principle followed by per-protocol analysis. Missing data will be handled using last-observation-carried-forward approach. Normality tests will be performed to determine the normal distribution of data. Two-way repeated measures ANOVA will be used for comparing the measured outcomes between two groups at different time points; chi-square tests are used to compare proportions for categorical variables. Non-parametric tests will be employed if normality assumption is violated. Additional sub-group analysis be explored and stratified by gender, BMI, and age. SPSS version 25.0 (IBM, NY, USA) will be used to perform analysis and significance level is set at $p<0.05$.

Data monitoring

All investigators will be responsible for record keeping. Only principle and co-investigators, authorized research personnel and Ethical Committee can access to the personal data during and after the study. All data collection will be performed with strict adherence to the professional standards of confidentiality. Any personal information, including participants' name, address, phone number etc, will be removed from all records. Important documents will be retained for at least 3 years after the completion of the study for final report and inspection.

Data Statement

Data and resources will be shared with other eligible investigators through academically established means. The protocol and datasets used or analysed in this study will be available

from the corresponding author upon reasonable request. Researchers who provide a methodologically sound proposal may access data to achieve aims in the approved proposal.

Patient and public involvement

Patients and the public were not involved in the design or planning of the study. Members of the public are involved in the recruitment of participants or conduct of the study. We will report test results to participants in plain language after their end-point assessments are completed. Results will be available to the public and patients in the forms of educational talks and booklets or flyers and published in open access peer-reviewed journals.

Ethics and dissemination

LMHFV is a non-invasive intervention and reported to have no serious adverse effect [6]. The only ethical concern is the additional DXA assessments, which emits a low-dose radiation at 10 microSv, roughly equivalent to 1 day exposure to natural background radiation.

DISCUSSION

To our knowledge, this is the first study to investigate the efficacy of low-magnitude high-frequency vibration therapy (LMHFV) on wheelchair users. As the worldwide ageing population escalates, the number of people with mobility impairment or disability would also increase[26]. These people would inevitably be relying on wheelchair to assist their daily living[27]. Wheelchair-bound elderlies usually have limited physical activity and is therefore associated to lower BMD[28] and ability to control body position, and thus have an increased risk of fall and osteoporotic fractures. A study from Grant Medical Center in the United States investigated 30

wheelchair-bound participants who fell from wheelchair over a 5 years period[29]. The report showed that elderlies who were older than 65 years of age with higher fall risk were associated with lack of physical activity and poor nutrition, leading to a decrease in muscle mass and strength. As most osteoporotic fractures are caused by combination of poor balance, falls, and deteriorating bone strength. Therefore, LMHFV is the proposed strategy to target musculoskeletal deterioration in wheelchair users for the prevention of more detrimental consequences.

LMHFV has previously been reported to have positive effects on reducing fall and fracture risks, enhancing muscle strength and improving balancing ability in healthy community-dwelling older people [6 30]. Supported with this evidence, it is therefore hypothesized that LMHFV would provide positive effects on the musculoskeletal health and physical performance in terms of BMD, muscle strength, balancing ability on elderlies with disability or mobility impairments who rely on wheelchairs for locomotion.

Vibration is a good treatment modality that is easy to implement for physically challenged patients, like wheelchair users. However, there is a scarce of literature reporting its effect on this group of patients who are most desperately in need of the treatment. There have been a few reports on the application of vibration treatment on wheelchair users with spinal cord injury (SCI). Menéndez's study reported in 2016 investigated the acute effect of whole-body vibration [17]. Ten patients with SCI were recruited and treated with various treatment schemes including the whole-body vibration (WBV). Patients were instructed to sit on wheelchairs with their feet rested on the vibration platform (Galileo Home, Galileo, Novotec, Germany, 10 Hz, 5 mm peak-to-peak). Their results have shown an enhancement to the mean blood velocity (MBV) and peak blood velocity (PBV) by approximately 25% at 7 minutes after a 1-minute vibration treatment. A

separate study in 2016, also by Menéndez's group, investigated the long-term combined treatment effect of WBV and electromyostimulatin (ES) in SCI patients. Seventeen participants with SCI were randomized into treatment group and control group for 12 weeks. Patients in treatment group received 30 sections of 10-minute WBV and ES stimulation over a 12-week period [16]. The treatment group was reported to show increased resting arterial diameter, increased blood flow, and increased muscle thickness at the gastrocnemius after 12 weeks of treatment. Although these studies employed a side-alternating vibration (instead of vertical-oscillating vibration) only to the lower limbs, these results suggested that mechanical stimulation in the form of vibration could provide benefits to blood flow that is associated with better performance-related outcomes in paralyzed skeletal muscles. Therefore, suggesting that the proposed LMHFV treatment, providing a vertical oscillating stimulation (Figure 1) to the whole-body would be beneficial to the target group of patients.

Findings of the current clinical trial would generate valuable data that is of high clinical translation values for wider application of vibration therapy in the community; and to generate clinical evidence that is not restricted to the healthy and mobile older people, but also to the group of patients with mobility impairments and high risk of further musculoskeletal function deterioration. Although the study only investigates the a treatment period of 6-months due to limited research resources, a longer or sustained use of the vibration treatment may be observed as suggested by our previous study that beneficial effects on healthy older adults are maintained even after 12-months of treatment cessation [30].

DECLARATION

Acknowledgements: This study was supported by Project Impact Enhancement Fund (Ref: PIEF/U3/01) and Evidence-Based Orthopaedics Clinical Education and Research Program (EBO) of the Chinese University of Hong Kong; V-health Limited for lending and modifications the vibration platforms used for this study. The authors declare no conflict of interest.

TRAIL STATUS

This trial is in process of planning participant recruitment.

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FUNDING

This study was supported by Project Impact Enhancement Fund (Ref: PIEF/U3/01) and Evidence-Based Orthopaedics Clinical Education and Research Program (EBO) of the Chinese University of Hong Kong; V-health Limited for lending and modifications the vibration platforms used for this study.

AUTHOR CONTRIBUTIONS

SKHC, YNC, RMYW, WHC conceptualized the study; SKHC, YNC, CYH drafted the manuscript; CYH, HWW execute the research project and data collection. All authors reviewed and approved the final manuscript.

ETHICS APPROVAL

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong (Ref. no 2019.087-T) and conformed to the Declaration of Helsinki. Results will be disseminated through peer-reviewed publications, conferences and workshops.

CONSENT FOR PUBLICATION

Not applicable.

ABBREVIATIONS

Low-magnitude high-frequency vibration (LMHFV)
Bone mineral density (BMD)
Areal BMD (aBMD)
X-ray absorptiometry (DXA)
Quality of life (QoL)
International Society for Clinical Densitometry (ISCD)
World Health Organization (WHO)
Center of pressure (COP)
36-item Short-Form Health Survey (SF-36)
Spinal cord injury (SCI)
Whole-body vibration (WBV)
Mean blood velocity (MBV)
Peak blood velocity (PBV)
Electromyostimulatin (ES)

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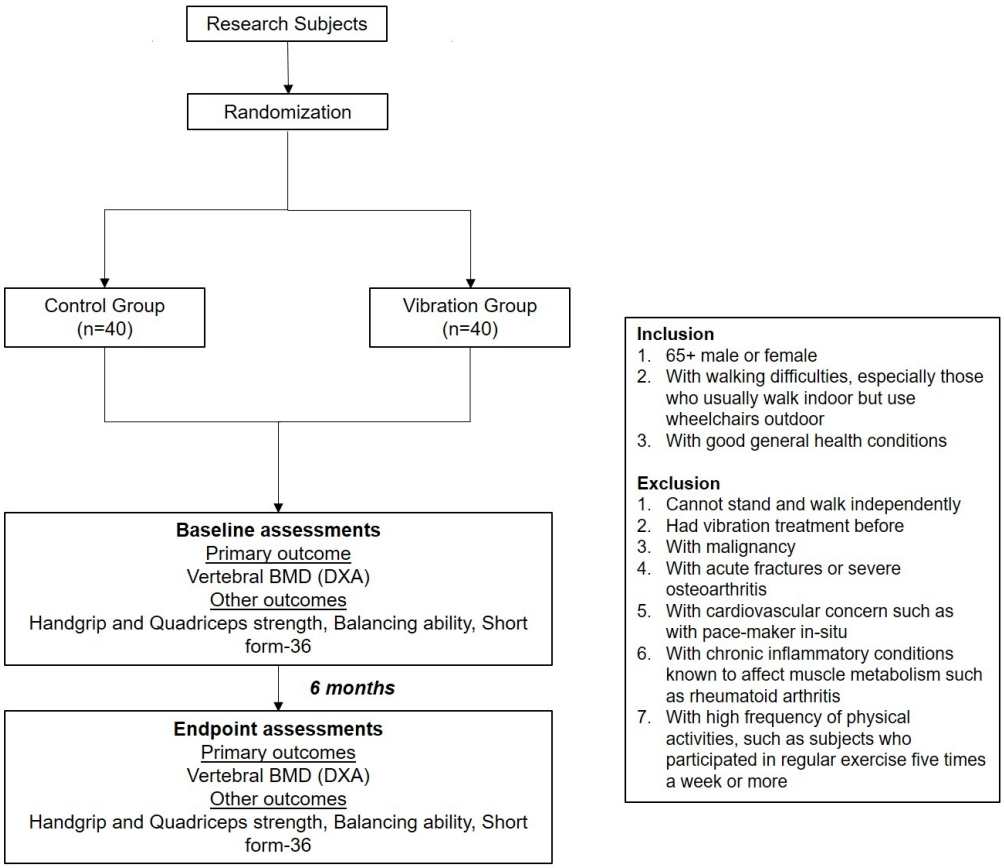
FIGURE LEGEND

Figure 1 Flow diagram showing the grouping and assessments in this study.

Figure 2 A vertical-oscillating vibration platform modified to provide a seating place for the research participant to receive the 20 min/day treatment. This representative vibration platform is installed in a community centre situated in a public housing estate with 6692 units/families in the Shatin district of Hong Kong.



Flow diagram showing the grouping and assessments in this study.

109x96mm (300 x 300 DPI)

A vertical-oscillating vibration platform modified to provide a seating place for the research subject to receive the 20 min/day treatment. This representative vibration platform is installed in a community centre situated in a public housing estate with 6692 units/families in the Shatin district of Hong Kong.

48x67mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	See this checklist
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	n/a
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	n/a

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4-5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-7; Figure 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	7

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-10

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	See comment

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed *(DMC is unlikely to have the opportunity to make a difference in this short term study where patient follow up is only 6 months and this study has minimal patient risk)*	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See uploaded document
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a