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High-Frequency, Low-Intensity Vibrations Increase Bone Mass and Muscle Strength in Upper Limbs, Improving Autonomy in Disabled Children

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ABSTRACT

Disuse osteoporosis in children is a progressive disease that can affect quality of life. High-frequency, low-magnitude vibration (HFLMV) acts as an anabolic signal for bone and muscle. We undertook a prospective, randomized, double-blind, placebo-controlled clinical trial to assess the efficacy and safety of regional HFLMV in disabled children. Sixty-five children 6 to 9 year of age were randomized into three groups: placebo, 60 Hz, and 90 Hz. In the two active groups, a 0.3-g mechanical vibration was delivered to the radii and femurs for 5 minutes each day. After 6 months, the main endpoint was bone mineral density (BMD) at the ultradistal radius (UDR), 33% radii (33%R), and femoral necks (FN). Secondary endpoints were area and bone mineral content (BMC) at the UDR, 33%R, and FN; grip force of the upper and lower limbs; motor function; and PedsQL evaluation. An intention-to-treat analysis was used. Fifty-seven children (88%) completed the protocol. A significant increase was observed in the 60-Hz group relative to the other groups in BMD at the UDR ($p = .011$), in grip force of the upper limbs ($p = .035$), and in the "daily activities item" ($p = .035$). A mixed model to evaluate the response to intervention showed a stronger effect of 60 Hz on patients with cerebral palsy on the UDR and that between-subject variability significantly affected the response. There were no reported side effects of the intervention. This work provides evidence that regional HFLMV is an effective and safe strategy to improve bone mass, muscle strength, and possibly independence in children with motor disabilities. © 2011 American Society for Bone and Mineral Research.

KEY WORDS: VIBRATION THERAPY; BONE MASS; MUSCLE STRENGTH; QUALITY OF LIFE; CHILDREN

Introduction

There is increasing evidence that high-frequency, low-magnitude vibration (HFLMV) serves as an anabolic signal to the musculoskeletal system, with clinical results showing improvements in bone mass, muscle strength, and balance.[1–4] Given the long-term complications of disuse osteoporosis in children,[5,6] these noninvasive mechanical signals—if shown to be effective—could help combat this bone and muscle loss and ultimately may benefit quality of life in the disabled. Ward and colleagues reported promising results of HFLMV on bone mass in a pilot study, in which 20 children were stimulated with whole-body HFLMV (90 Hz at 0.3 g, where 1 g is earth's gravitational field, or 9.8 m/s^2) for 10 minutes each day over a 6-month period. This study showed a net benefit to volumetric trabecular bone mineral density (BMD) in the proximal tibia, but neither diaphyseal bone nor muscle mass muscle parameters showed any response to the mechanical signals. However, this study also had several important weaknesses that may have influenced the outcomes—the heterogeneity in age and pubertal status of the subjects within the intervention and control groups and the low compliance, attributable to the degree of difficulty of standing on the platform.[7] More recently, Ruch and colleagues reported a small pilot study using whole-body vibration to treat children with cerebral palsy (CP), with results indicating a *decrease* in bone quality in the treated group but a small increase in walking speed. These investigators used mechanical vibration parameters that were distinct from those used in the Ward trial, with a protocol of high-magnitude vibration (6 mm at 18 Hz, delivering 7.8 g) at relatively low frequencies (12 to 18 Hz) and with

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compliance compromised by complaints of fatigue and/or pain.[8] Together, these studies indicate the potential benefits of a nondrug anabolic intervention for musculoskeletal complications of a disabled pediatric population but with full recognition that there could be limitations to the use of such interventions. Therefore, the aims of this study were to assess the effectiveness and safety of the regional use of HFLMV in a randomized, double-blind, controlled trial in children 6 to 9 years of age with motor disabilities.

Methods

Study protocol and subjects

A randomized, double-blind, placebo-controlled study was conducted from January 2005 to June 2007. Sixty-five children with motor disabilities from the Telethon Rehabilitation Institute and Neurorehabilitation Unit of Catholic University, Santiago, Chile, were recruited to participate. This protocol was reviewed and approved by the ethics committee of our institution, and all legal guardians provided written informed consent.

Inclusion criteria

Prepubertal boys and girls aged 6 to 9 years with motor disabilities caused by a first- or second-order neuron disease, myopathies, or peripheral nerve disease were recruited. To be included, the subject had to be able to sit and had to have an IQ greater than 70. It was also required that the *Z*-score of the BMD of the femoral neck (FN) be less than −1.5 in at least one limb, according to the values defined by Chilean healthy children reference values.[9]

Exclusion criteria

Subjects were excluded if they had any of the following: (1) malnutrition, (2) constitutional, endocrine, or bone disease other than low BMD, (3) a requirement of chronic medication (particularly anticonvulsant, glucocorticoid, or bisphosphonate medications), (4) low calcium intake based on the Recommended Daily Allowances (RDAs), (5) 25-hydroxyvitamin D [25(OH)d] concentration less than 15 ng/mL, (6) parathyroid hormone (PTH) concentration greater than 45 pg/mL, (7) thyroid-stimulating hormone (TSH) concentration greater than 4 UI/mL, (8) alkaline phosphatase concentration greater than 300 UI/mL, and (9) joint contractures or involuntary movements (eg, spasticity) that prevented adequate and reproducible positioning for dual-energy X-ray absorptiometry (DXA) measurement.

Biochemical measurements

At the start of the study, blood samples were drawn for 25(OH)D, PTH, TSH, serum calcium, phosphate, total alkaline phosphatase, albumin, and transaminase measurements. The protocols have been published elsewhere.[10,11]

Densitometry

BMD, bone mineral content (BMC), and bone areas at the ultradistal radius (UDR), 33% radii (33%R), and FN were evaluated at baseline and at the end of the protocol by DXA (Lunar Prodigy) using eENCORE Software 2004, Version 845.006 (Lunar Corp., Madison, WI, USA). For all regions of evaluation, the manufacturer's software was used with the low-intensity scan protocol. The BMC precisions determined using a 15-subject sample were 1.67% for UDR, 1.89% for 33%R, and 2.52% for FN.

Muscle strength and motor function evaluation

Three standardized and validated measures were used: the dynamometric muscular strength measure and two functional tests, the Gross Motor Function Measure (GMFM)[12–14] and the Motor Function Measure (MFM).[15,16] The GMFM assesses the gross motor abilities of children with CP and MFM of children with neuromuscular diseases. The scores of both scales were transformed into a percentage of the maximum score, and these percentages were analyzed together as a representation of motor function. Functional testing and dynamometric evaluation were conducted by two physical therapists who had experience with the management and evaluation of patients with CP and neuromuscular diseases. A calibrated digital handheld dynamometer (Nicholas MMT, Model 01160, and Baseline hand dynamometer, Model 01163, Lafayette Instrument Co., Lafayette, IN, USA) was used. Maximum isometric contraction values were measured in 11 different muscle groups (ie, shoulder abductors and flexors, elbow flexors and extensors, wrist extensors, grip, hip flexors and abductors, knee extensors and flexors, and foot dorsiflexors) by using the "break" technique,[17,18] in which the examiner gradually overcomes the muscle force and stops at the moment the extremity gives way. The highest value of the three contractions with an interval of at least 30 seconds was recorded for each group. In our laboratory, interrater reliability (interclass coefficient) for all measurement was more than 0.71 (SEM 5.8%), and test-retest reliability was more than 0.81 (SEM 5.2%). Average values were calculated for the upper and lower limbs separately, which included proximal and distal muscle groups. This average was reported and used in the statistical analysis.

Quality-of-life evaluation

At baseline and at the end of the protocol, the quality of life in the subjects was evaluated by PedsQL using the CP module for all children. This module includes the following items: daily activities, school activities, movement and balance, pain and hurt, fatigue, eating activities, and speech and communication.[19] The questionnaire was validated for use in Chilean children.

Intervention

To produce an axial propagation of vibration through the radii or femurs, a high-frequency, low-intensity vibration device, active at either 60 or 90 Hz and with displacements of the actuator of 100 μm, was placed on both elbows and knees (limbs at an angle of 90 degrees). The HFLMV device was pressed onto the limb and held at the region of interest by wrapping with an elastic band and Velcro. The guardians of each subject were trained to use the device for 5 minutes on each limb, 7 days a week, for 6 months. The devices were programmed to stop automatically following 5 minutes of use. The devices could be set up in the placebo or active mode. In the placebo mode, the device produced a 500-Hz

noise but did not vibrate. The devices were able to record the number of sessions, the duration, and the dates and times of use. This information was used to assess compliance. This device (Fig. 1) acts by acceleration and not by an action-reaction mechanism because this is not a weight-bearing device. This device allows the displacement and frequency to be set independently; hence, when frequencies of 60 or 90 Hz were used, the amplitude always was 100 μm.

Safety

Reporting of any minor adverse events was recorded by a monthly phone call request. Participants and their guardians were advised to report any serious adverse events immediately and to stop use of the device. The number and days of hospitalization and episodes of intercurrent disease were recorded monthly. The hospital review board was advised that according to ISO-2631, "Threshold Advisory for Human Exposure to Whole Body Vibration," vibration of the magnitude/frequency delivered by the HFLMV device was considered safe for up to 4 hours each day.

Statistics

The primary endpoint measures included BMD at the UDR, 33%R, and FN. Secondary endpoint measures included BMC and bone area at these sites, upper extremity muscle strength, and quality-of-life score. Power calculations were based on data from a similar pilot study.[7] A sample size of 54 (three groups of 18 subjects) was required to detect a 15% difference with 80% power at the $p = .05$ level. We recruited 65 subjects, allowing for a 15% dropout rate. We analyzed data using an intention-to-treat approach comprising all randomized subjects.

All variables were expressed as the median ± range to account for nonnormal distributions. Statistical analysis was performed using SPSS 10.0 for Windows (SPSS, Inc, Chicago, IL, USA), with differences assessed by the Kruskal-Wallis test. Right and left radii variables were analyzed separated; the same was done for the femurs. Thus the sample unit was the radii and femurs. A variable that indicated that these two radii and femurs belong to the same subject was included in the analysis. The effect of clinical variables on the response to the HFLMV intervention was evaluated using a linear mixed model. The strength and direction of the linear relationship between two continuous variables was assessed with a Spearman correlation. A linear mixed model was performed to explain how the intervention affected the percentage of change in outcomes and the influence of clinical variables on this change. A p value less than .05 was considered statistically significant.

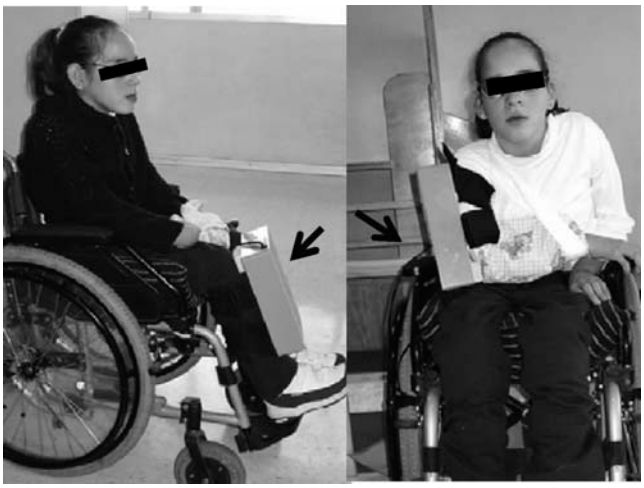

Fig. 1. A child undergoing stimulation of the radius (*A*) and femur (*B*) using the device (*arrows*).

Results

Baseline comparisons of the three groups are shown in Table 1. There were significant differences between groups with respect to gender distribution. In the mixed model, the effect of the HFLMV intervention was not influenced by gender, so no post hoc adjustments were made. Databases from the two participating institutions were filtered by age, diagnosis, and IQ. A total of 101 subjects were contacted. During the phone call, the eligibility criteria were evaluated. Eighty-three subjects met the inclusion criteria and were invited to participate. Of those who completed the protocol, the primary afflictions included the following: cerebral palsy (CP, 39), spinal muscular atrophy (3), Duchenne muscular dystrophy (9), congenital myopathies (3), and axonal polyneuropathy (3). Eleven of 57 children (19%) had sustained at least one fracture in the appendicular skeleton at least 6 months prior to enrollment.

Flow diagram of the study

A flow diagram of the progress of screened subjects and randomization is shown in Fig. 2. Sixty-five children were enrolled in the study, and 61 met the biochemical and densitometric criteria. Fifty-seven children completed the 6-month protocol (93.4%). Two subjects in the 60- and 90-Hz groups withdrew because of the absence of any positive change, as observed by their parents.

Changes in BMD

As compared with baseline, the UDR BMD value of the 60-Hz group increased 31.88% ± 28.30%, which represented a significant increase above that in the placebo and 90-Hz groups ($p = .011$; Table 2, Fig. 3). In contrast, the UDR BMC value in the 90-Hz group increased 6.42% ± 14.32%, which also represented a significant increase above that in the placebo and 60-Hz groups ($p = .035$). We did not observe any other significant differences in 33%R or FN.

In the 60-Hz group, the percentage changes in the UDR and 33%R BMD values were negatively correlated with the baseline values ($r = -0.148$, $p = .05$, and $r = -0.447$, $p = .0001$, respectively). Additionally, the bone area at the UDR and 33%R correlated negatively with the initial values ($r = 0.362$, $p = .0001$, and $r = -0.311$, $p = .001$, respectively). We did not find any significant correlations for the 90-Hz group.

Table 1. Clinical Characteristics of the Subjects at Baseline

Item	Placebo ($n = 21$)	60 Hz ($n = 22$)	90 Hz ($n = 18$)	p Value
Age (years)	9.14 ± 1.42	8.46 ± 2.05	8.37 ± 1.11	.270
Sex (F/M)	5/16	10/12	10/8	.041
Weight (kg)	31.89 ± 8.95	24.86 ± 6.49	27.25 ± 7.90	.678
Height (m)	129.43 ± 9.76	121.76 ± 11.34	125.83 ± 8.95	.967
BMI (kg/m^2)	18.73 ± 3.45	16.46 ± 2.31	16.92 ± 3.27	.433
BMD UDR (g/cm^2)	0.23 ± 0.05	0.22 ± 0.03	0.23 ± 0.04	.061
BMC UDR (g)	0.58 ± 0.24	0.55 ± 0.17	0.59 ± 0.17	.077
Area UDR (cm^2)	2.75 ± 0.49	2.52 ± 0.530	2.52 ± 0.52	.296
BMD 33%R (g/cm^2)	0.41 ± 0.07	0.37 ± 0.07	0.40 ± 0.05	.072
BMC 33%R (g)	0.84 ± 0.21	0.75 ± 0.23	0.81 ± 0.31	.346
Area 33%R (cm^2)	1.91 ± 0.27	1.93 ± 0.52	1.73 ± 0.39	.296
BMD FN (g/cm^2)	0.652 ± 0.153	0.593 ± 0.114	0.643 ± 0.157	.372
BMC FN (g)	1.45 ± 0.81	1.00 ± 1.38	1.26 ± 0.46	.141
Area FN (cm^2)	2.08 ± 0.72	1.67 ± 0.48	1.87 ± 0.51	.171
First neuron/second neuron/other disease (n)	18/1/2	19/1/2	14/2/2	.457
Motor function (%)	69.99 ± 23.88	45.90 ± 21.79	63.12 ± 28.55	.558
Muscle strength (kg), upper limbs	4.04 ± 2.06	1.94 ± 1.82	2.50 ± 2.14	.168
Muscle strength (kg), lower limbs	4.88 ± 2.04	2.16 ± 2.51	3.48 ± 2.94	.162
Alkaline phosphatase (IU/L)	214.14 ± 78.58	215.1 ± 62.17	233.79 ± 82.62	.791
25(OH)D, ng/mL	19.61 ± 4.07	21.39 ± 7.83	20.54 ± 8.00	.091
PTH, pg/mL	39.73 ± 14.51	30.45 ± 14.46	36.06 ± 13.16	.179
TSH, μU/L	2.31 ± 0.92	2.73 ± 1.17	2.91 ± 1.42	.445

Changes in motor function and muscle strength

Muscle forces measured at upper and lower limbs were evaluated independently. At 6 months (and compared with baseline), the average muscle forces measured for the upper limbs increased by $165.27\% \pm 64.81\%$ in the 60-Hz group, whereas in the placebo and 90-Hz groups, the average muscle forces decreased by $-19.98\% \pm 49.98\%$ and $-5.27\% \pm 94.26\%$, respectively ($p = .035$; Fig. 3, Table 2). In contrast, the muscle strength at the lower limbs did not change significantly in any of the groups.

The percentage change in the motor function score in the three groups correlated positively with the following parameters: the percentage change in 33%R BMD ($r = 0.693$, $p = .004$), 33%R BMC ($r = 0.679$, $p = .005$), and UDR area ($r = 0.73$, $p = .001$). The percentage change in the UDR BMD correlated positively with percentage change in abduction and flexion strength at the upper limbs ($r = 0.739$, $p = .002$, and $r = .674$, $p = .006$, respectively). Additionally, the percentage change of the UDR BMC correlated with the percentage change in abduction strength of the upper limbs ($r = 0.579$, $p = .024$). There were no significant correlations between muscle strengths and densitometric variables for the lower limbs.

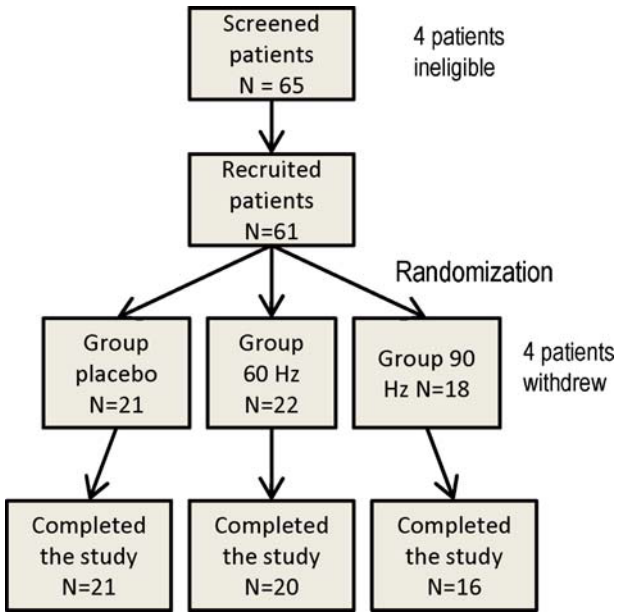

Fig. 2. Flowchart summarizing the experimental design and the distribution of the participants following screening and randomization.

Changes in quality-of-life assessment

Changes in the PedsQL scores are shown in Table 3. The average score change was not significantly different, but the change in the "daily activities item" score was significant. The "daily activities item" included questions about how many problems the child had with the following: putting on shoes, buttoning a shirt, pulling a shirt on over the head, putting pants on, brushing the hair, getting into the bathroom to use the toilet, undressing to use the toilet, getting in and out of the bathtub/shower, and brushing the teeth. Thus the "daily activities item" assesses autonomy.

Table 2. Percentage Change From Baseline in Outcomes and Comorbidity

Item, % change	Placebo ($n = 21$)	60 Hz ($n = 22$)	90 Hz ($n = 18$)	p Value
BMD UDR	0.90 ± 19.05	31.88 ± 28.30[a]	5.20 ± 8.63	.011
BMC UDR	-1.35 ± 18.21	-0.01 ± 30.78	6.42 ± 14.32[b]	.035
Area UDR	-4.43 ± 25.67	2.55 ± 30.07	1.60 ± 20.56	.490
BMD 33%R	7.33 ± 10.99	11.58 ± 14.78	7.10 ± 8.14	.160
BMC 33%R	7.33 ± 10.99	11.58 ± 14.78	7.10 ± 8.14	.060
Area 33%R	-4.43 ± 15.82	2.55 ± 12.76	1.60 ± 21.23	.346
BMD FN	1.66 ± 31.26	1.59 ± 10.34	2.42 ± 36.73	.703
BMC FN	-6.49 ± 21.21	-5.23 ± 40.34	-11.18 ± 38.78	.177
Area FN	-7.84 ± 32.56	-2.20 ± 50.85	-9.72 ± 54.14	.140
Motor function (%)	-3.25 ± 4.80	1.41 ± 6.10	1.03 ± 13.78	.078
Muscle strength, upper limbs	-19.98 ± 49.89	165.27 ± 64.81*	-5.27 ± 94.26	.035
Muscle strength, lower limbs	8.82 ± 64.03	76.21 ± 114.44	70.32 ± 96.71	.441
Hospitalization days	0.27 ± 0.62	0.10 ± 0.05	0.44 ± 0.65	.142
Intercurrent diseases (n)	0.86 ± 0.57	0.10 ± 0.06	0.31 ± 0.51	.138

[a]The 60-Hz group was significantly different from the placebo and 90-Hz groups.
[b]The 90-Hz group was significantly different from the placebo and 60-Hz groups.

Compliance and adverse events

Average compliances in terms of number of sessions prescribed were $34.92\% \pm 32.92\%$, $35.91\% \pm 28.36\%$, and $42.13\% \pm 25.47\%$ ($p = .547$) for the placebo, 60-Hz, and 90-Hz groups, respectively. The averages in terms of total time prescribed were $28.04\% \pm 26.96\%$, $31.62\% \pm 25.73\%$, and $34.22\% \pm 23.31\%$ ($p = .599$) for the placebo, 60-Hz, and 90-Hz groups, respectively. Compliance did not affect the response to intervention, as evaluated by a mixed model. No side effects were reported in any of the three treatment groups. During the 6-month intervention, there were no significant differences in hospitalization days (placebo: 6/22; 60 Hz: 2/20; and 90 Hz: 7/16; $p = .14$) or the number of intercurrent diseases (placebo: 19/22; 60 Hz: 2/20; and 90 Hz: 5/16; $p = .13$) among the groups.

Effect of clinical variables on the response to intervention

The results are shown in Table 4. Age, sex, weight, height, body mass index (BMI), vitamin D status did not affect the response to therapy. The baseline value significantly affected the response to the intervention; thus the model was adjusted to take into account the initial values ($p < .0001$). The influence of the mechanical intervention on BMD and BMC was stronger with the 60-Hz signal than with the placebo or the 90-Hz signal (estimation 34.18%, $p < .0001$); in contrast, 60 Hz and 90 Hz were not different from placebo with respect to area. The effect of the intervention on BMC, BMD, and body area was greater at the UDR than at the 33%R (estimation 27.45%, $p < .0001$; estimation 12.34%, $p < .0001$; estimation 3.5%, $p < .0012$, respectively). Additionally, the responses in BMD, BMC, and body area were stronger in children with CP than in children with other diseases (estimation 26.51%, $p = .0001$; estimation 9.84%, $p < .0001$; estimation 4.24%, $p = .012$, respectively); the responses also were stronger for left-side limbs for BMD and BMC (estimation 0.52%, $p = .023$; estimation 0.46%, $p = .01$, respectively). The between-subject variability significantly affected the response to the intervention with respect to BMD and BMC (estimation 7.43%, $p = .011$; estimation 5.18%, $p = .013$, respectively). There was no significant effect of therapy on FN.

Discussion

This study demonstrates that high-frequency, low-magnitude vibration can improve bone mineral density, muscle strength, and ultimately, autonomy for children with disabling conditions. Importantly, this study emphasizes that these mechanical signals can be delivered to specific regions of the appendicular skeleton rather than requiring exposure to whole-body vibration, which would limit use to patients who are ambulatory. We believe that these data provide evidence that this nondrug, noninvasive intervention is both safe and effective and ultimately could provide a means to strengthen the musculoskeletal system of patients who are not mobile. Although the mechanism of action is not known and compliance was far from ideal, these data support the hypothesis that mechanical signals need not be large to be effective, nor do they have to be endured for long periods of time. Because there were no reported complications of use, we are hopeful that these data provide supportive evidence for translating this biomechanical strategy into the clinical setting as a means of reducing the risk of fracture and building independence for children.

Moreover, this is the first study proposing regional rather than total-body stimulation. This kind of stimulation facilitates the use of this intervention on the upper limbs, which is not possible with total-body vibration.

The studies of Garman and colleagues[20] and Hwang and colleagues[21] showed that bone does not need to be loaded to be responsive to mechanical signals, and thus it may be that osteoblasts and their progenitors (mesenchymal stem cells) are sensitive to acceleration, thus facilitating application of the HFLMV signal. Our study supports these findings in a clinical setting. We observed a more significant effect on the UDR than

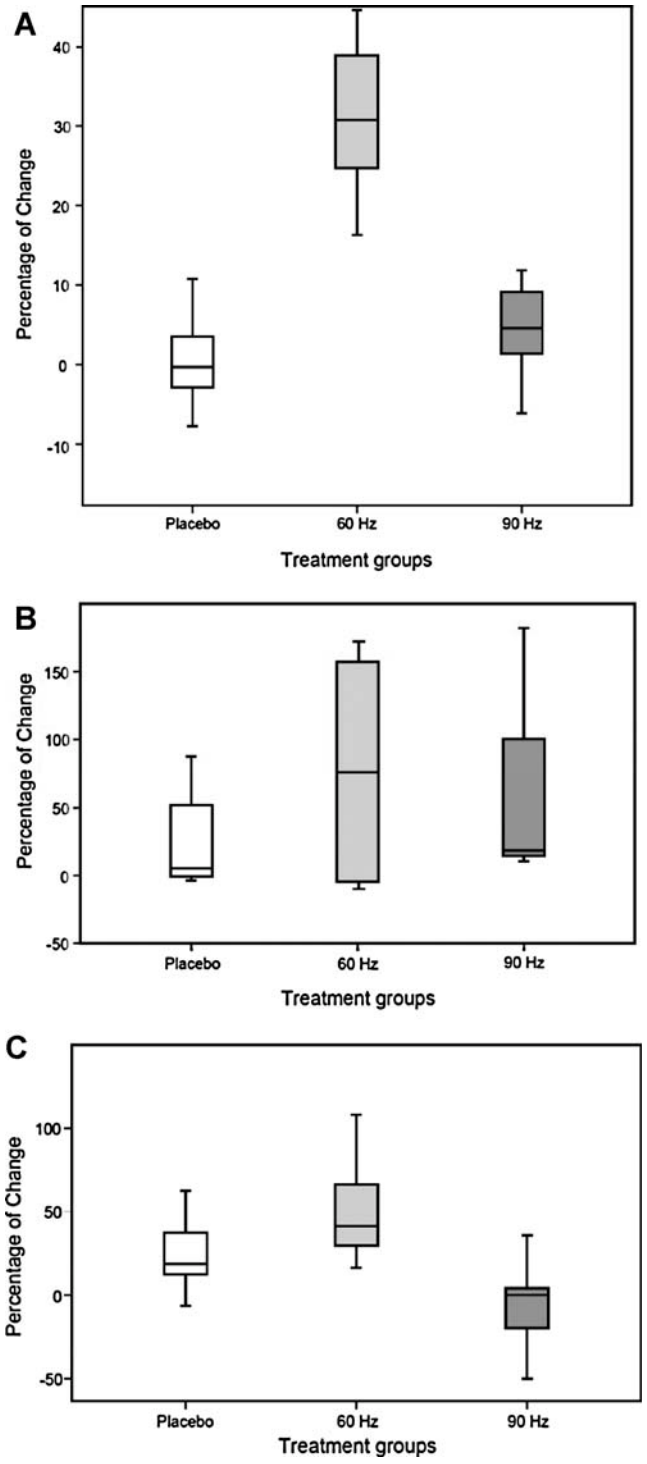

Fig. 3. (*A*) Percentage change from baseline in URD BMD; the 60-Hz group was significantly different from the other groups ($p = 0.011$). (*B*) Percentage change from baseline in grip strength of the upper limb; the 60-Hz group was significantly different from the other groups ($p = .045$). (*C*) Percentage change from baseline in the PedsQL "daily activities" scores; the 60-Hz group was significantly different from the other groups ($p = .046$).

on the 33%R and FN scores, which suggests a stronger effect on trabecular bone than on cortical bone. However, not all but most studies in animals and humans are in agreement with a greater effect on trabecular bone.[22–24]

Notably, a stronger effect in children with CP (first-order neuron disease) could indicate the importance of the indemnity of second neurons or peripheral innervations on the mechanical stimulation of osteogenesis. Sample and colleagues have reported that the innervation of bone could be a critical mediator of Wolff's skeletal adaptation to mechanical signals. The authors demonstrated that an intense mechanical stimulus can translate to the contralateral control limb, and innervation is critical to the transformation of local loading into an adaptive event.[25]

A stronger effect of HFLMV on the left-side limbs could represent a confounder because the left-side limbs showed lower baseline BMD and BMC values, and a negative correlation was found between the initial value and the percentage change.

We observed a stronger effect on bone and muscle strength in the 60-Hz group. Bone response, as evaluated by bone histomorphometry, is not linearly correlated with frequency. A review of animal studies showed that the optimal frequency appears to be around 50 Hz. Between 10 and 50 Hz, there is no significant difference in bone histomorphometric parameters. However, very low (1 Hz) and high (100 Hz) frequencies are significant less effective than the 10- to 50-Hz range. Thus the stronger effect of 60-Hz stimulation in this work is in agreement with animal studies' experience.[26,27]

HFLMV did not have a significant effect on densitometric or strength parameters at the FN. In this protocol, evaluation at the FN may not be the best place to see the effect on mineralization. Evaluation of densitometric parameters at the distal lateral femur, a site mostly composed of trabecular bone and a frequent site of fracture in these children, would be a better site to assess the effect of HFLMV.[28] Another possible explanation is that we did not stimulate in the correct way. The signals may not have been transmitted or may have been damped out by sitting.[29] Future studies could examine different frequencies, displacements, and assessment tools.

The work reported herein helps to emphasize that the frequency, amplitude, duration, and transmission of vibration are all important variables that contribute to the anabolic response in muscle and bone.[22,24] We demonstrated that subject variability significantly modified the response to HFLMV. In agreement, studies in the clinic[7] and laboratory[24] have emphasized that genetics and subject variability play critical roles in mechanosensitivity and the response to treatment. Of note, the benefit on muscle strength appears to be more consistent across studies.[30–34] Xie and colleagues have shown that these mechanical signals are anabolic to both bone and muscle.[35] However, a synergy has been demonstrated between muscle and bone mass and strength.[36,37]

We observed a significant negative correlation between the percentage BMD change and the initial value. This finding also has been reported for antiresorptive therapy. HFLMV may be more effective in more osteoporotic children. Thus even this small signal may be sufficient to mobilize the adaptive response in bone.

A significant improvement in the "daily activities item" of the PedsQL questionnaire was observed, although this study did not have sufficient power to assess this outcome. This improvement emphasizes the importance of bone mass on

Table 3. Effects of the Intervention on Percentage Change in BMD, BMC, and Area and the Influence of Clinical Variables on This Change

	% Change in BMD		% Change in BMC		% Change in area	
Variable	Estimation	*p*	Estimation	*p*	Estimation	*p*
Treatment group						
Placebo	0[a]		0[a]		0[a]	
60 Hz	34.18	<.0001	11.32	.020	6.23	.041
90 Hz	0.34	NS	0.000	<.0001	−0.27	NS
Diagnosis group						
1 (1st neuron)	26.51	<.0001	9.84	<.0001	4.24	.012
2 (others)	0[a]		0[a]		0[a]	
Radius site						
UDR	27.45	<.0001	12.34	<.0001	3.5	<.012
33%R	0[a]		0[a]		0[a]	
Body side						
Right	0[a]		0[a]			
Left	0.52	.023	0.46	.03	0.01	NS
Between-subject variability	7.43	.011	5.18	.013	1.25	NS

Note: Results of the linear mixed model.
[a]The 60-Hz group was significantly different from the placebo and 90-Hz groups.

Table 4. Percentage Change from Baseline in PedsQL Scores

Item	Placebo, % ($n = 21$)	60 Hz, % ($n = 22$)	90 Hz, % ($n = 18$)	*p* Value
Daily activities	21.18 ± 72.28	46.52 ± 104.39[a]	-17.85 ± 51.26	.046
School activities	6.85 ± 12.55	1.17 ± 10.11	3.64 ± 15.00	.447
Movement and balance	-12.89 ± 20.88	-5.96 ± 22.62	2.56 ± 12.42	.083
Pain and hurt	3.40 ± 11.40	6.43 ± 13.77	4.03 ± 14.25	.832
Fatigue	6.07 ± 12.51	11.58 ± 14.78	7.10 ± 8.14	.278
Eating activities	6.92 ± 11.68	4.30 ± 7.43	2.72 ± 11.32	.506
Speech and communication	0.99 ± 6.85	1.93 ± 10.12	0.18 ± 14.61	.828
Total score	19.13 ± 27.56	11.90 ± 24.73	-2.20 ± 29.83	.234

[a]The 60-Hz group was significantly different from the placebo and 90-Hz groups.

motor performance. Additionally, pamidronate has been shown to improve motor abilities in children with osteogenesis imperfect.[38] The improvement in independence observed in these children is in agreement with the strong increase in muscle strength at the upper limbs demonstrated in this study. Thus enhanced mobility could contribute to bone mass and muscle strength in a virtuous cycle. An increase in autonomy is a primary clinical goal that has a major impact on the life of these children.

The strengths of this study were as follows: (1) the homogeneity of subjects in terms of age, anthropometry, and pubertal stage, (2) the strict eligibility criteria that controlled for most variables affecting growth and mineral accretion, (3) the new way of delivering mechanical signals, and (4) the compilation of muscle, bone, and quality-of-life data to determine whether this treatment could benefit autonomy.

The limitations of this study were as follows: (1) a sample size that was too small and a duration that was too short to study the effect of HFLMV on the fracture rate, (2) the patients were not evaluated by computed tomography, which could better evaluate the effect of HFLMV on true volumetric density and on bone geometric and mechanical variables, and (3) evaluation of the mechanical signal and how it was delivered (transmissibility) to the regions of interest could have been more comprehensive.

In summary, this work demonstrated that the use of HFLMV is an effective and safe therapy to improve bone mass and muscle strength as well as indices of autonomy in children with motor disabilities. The improvement in independence likely was possible owing to the innovation of regional use.

Disclosures

All the authors state that they have no conflicts of interest.

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