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Vibration-Assisted Home Training Program for Children With Spinal Muscular Atrophy

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Abstract

The aim of this study was to determine the effect of a new method of vibration-assisted neuromuscular rehabilitation in patients with spinal muscular atrophy types II and III. In this retrospective observational study, 38 children (mean age: 4.64 ± 1.95 years) were analyzed. The physiotherapy program, *Auf die Beine*, combines 6 months of home-based side-alternating whole-body vibration with interval blocks of intensive, goal-directed rehabilitation: 13 days at the start and 6 days after 3 months. Assessments were applied at the beginning (M0), after 6 months of home-based training (M6), and after 6 months of follow-up (M12). Motor abilities were assessed by the Gross Motor Function Measure 66 and Hammersmith Functional Mobility Scale. The Gross Motor Function Measure showed an increase of 1.69 (3.73) points ($P = .124$) and the Hammersmith Functional Mobility Scale a significant increase of 2.73 ± 1.79 points ($P = .007$) after 12 months; however, whether this leads to a long-term clinical benefit requires further investigation.

Keywords

children, developmental disability, efficacy, pediatric, rehabiliation

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Spinal muscular atrophy is an autosomal recessive neurodegenerative disease characterized by the loss of spinal cord motor neurons which leads to denervation, muscle weakness, and progressive loss of motor function. Spinal muscular atrophy is one of the most common autosomal recessive disorders with an incidence of about 1:10 000.[1–3] Homozygous deletions of the *survival motor neuron gene 1* (*SMN1*) have been identified as the most frequent disease-causing mutations. Furthermore, copy number variations of the *SMN2* gene modify the amount of SMN protein produced and thus affect the severity of the phenotype.[4,5] The excessive early death of motor neurons is linked to a complex disturbance in RNA metabolism resulting in alterations of neuronal trophic factors, altered neuromuscular end plates, and abnormal regulation of apoptosis, that is, programmed cell death.[6,7]

The less progressive forms of spinal muscular atrophy are types II (intermediate form) and III (juvenile, Kugelberg-Welander syndrome).[3] Motor milestones such as sitting and walking can be achieved during the first years of life but lost due to the progressive nature of the disease. It is often difficult to differentiate whether loss of function is due to progression of the disease itself, growth of the child, or secondary factors, for example, immobilization.[6–9]

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Recently, exon inclusion therapy by the use of splice-switching antisense oligonucleotides has been shown to be efficacious in restoring the primary defect by inducing a higher percentage of functional SMN protein from the SMN2 transcript (nusinersen for spinal muscular atrophy type I and II).[10] This approach has been successful to counteract the primary disease mechanism, specifically death of the motor neuron. However, even oligonucleotide therapy does not fully restore the SMN protein, and approaches are needed to address deterioration of muscle strength which leads to atrophy, decreased mobilization, alteration of bone, and altered neuromuscular interaction.[11,12]

Evidence in spinal muscular atrophy animal models and adults with spinal muscular atrophy suggests exercise as potentially beneficial to stabilize and improve muscle strength and motor function.[13–17] Charbonnier[15] reported benefits of regular exercise in spinal muscular atrophy mouse models for life span increase, improvement in motor capacity, and motor neuron survival. Grondard et al[14] showed that regular exercise (treadmill) prolongs survival in type II spinal muscular atrophy mice. Fletcher et al[18] recently showed that reduced proprioceptive synaptic input leads to motor neuron dysfunction in a spinal muscular atrophy mouse model.

Physiotherapy is well accepted as an important part of the interdisciplinary treatment of patients with spinal muscular atrophy, but there is no consensus and a lack of controlled trials to address frequency, intensity, or timing. Two studies recently investigated endurance training in patients with spinal muscular atrophy. Montes et al (2015) reported that daily exercise (6-month home-based cycling and strengthening) is safe in ambulatory patients with spinal muscular atrophy (14 participants, 10-48 years old).[19] Madsen et al (2015) demonstrated that a 12-week ergometer training improved oxidative capacity, but not function, in 6 patients with spinal muscular atrophy type III.[20] Older studies reported positive effects of functional electrical stimulation and high-resistance weight training in adults with spinal muscular atrophy.[21,22] Gains in strength were correlated with neural adaptation rather than muscle hypertrophy in these studies. Only 1 recent study reported on resistance training specifically in pediatric patients with spinal muscular atrophy, showing the feasibility and safety of a 12-week, home-based, 3 d/wk progressive resistance training program in 9 children.[13]

Based on this background, we suggest that exercise can not only improve or harness motor function but can also prevent long-term effects of immobilization such as osteoporosis and fractures. The actual impact, however, of physical training programs on motor outcomes in spinal muscular atrophy has received little attention in the literature.

Whole-body vibration has recently raised clinical and scientific interest as an effective, safe, and time-effective method to improve neuromuscular interactions in children and adolescents with neuromuscular diseases. Whole-body vibration induces reflex-based muscle contractions, which has the advantage of producing involuntary muscle contractions, and therefore provides afferent feedback mechanisms. It has been used frequently in adults and children with and without disabling conditions with positive results on muscle and bone and without serious side effects.[23–26] Vibrations are applied through a vibrating surface that mechanically stimulates the person on the platform and induces reflex-based muscle contractions.[27–30] The duration of a typical whole body vibration session is 3 times 3 minutes (9 minutes in total with breaks after every 3 minutes), at a frequency of 20 Hz which implies 10 800 mechanical impulses to the trained muscles (similar to 3 hours of walking).[30] Benefits of adding whole body vibration to traditional rehabilitation are faster gains of muscle function (because more muscle stimulation cycles can be applied in a shorter time) and safe exercise (reduced risk of falls in a controlled training position).[30]

Acute effects of whole body vibration in adults are reported as increased muscle temperature, oxygen consumption, and skin blood flow and long-term effects as reduced muscle and bone loss during immobilization, reduced falls, and improved balance.[30] Effects on EMG activity and depression of H-reflex have been shown in healthy adults and children with cerebral palsy.[29,31]

Combining side-alternating whole body vibration with intensive, functional, and goal-directed physiotherapy has shown that home programs combined with whole body vibration might be safe, feasible, and potentially effective.[24,32–34] Safety and feasibility in children with neuromuscular disorders (Duchenne muscular dystrophy and spinal muscular atrophy) have been systematically tested and found to be well tolerated and safe.[35]

Whole body vibration might have a potential benefit for patients with spinal muscular atrophy because it is activating muscle spindles and stimulating α motor neurons through 1a afferent fibers[29,31,36]; therefore, it can have a neuroprotective effect. Based on this rationale, we have established a neuromuscular rehabilitation program including whole body vibration *Auf die Beine*. The program consists of a combination of 2 short, intensive inpatient stays (interval rehabilitation) combined with 6 months of home-based whole body vibration training.

In this retrospective analysis, we present the results for motor function after participation in the program *Auf die Beine* (optional routine procedure of the German health-care system) for patients with spinal muscular atrophy type II and III at baseline, after 6 months of home-based whole body vibration training combined with intensive functional training, and additional 6 months of follow-up. The aim was to assess the safety and possible benefits to enable future controlled studies on whole body vibration and exercise studies for patients with spinal muscular atrophy.

Methods

This is an observational, retrospective analysis of the neuromuscular physiotherapy program *Auf die Beine* (University Hospital Cologne, Germany). The rehabilitation program *Auf die Beine* is part of the German health-care system and covered by insurance; however, participation in the program is optional and additional to the standard of care. We retrospectively analyzed children participating in the program *Auf die Beine* between March 2007 and March 2017. Figure 1

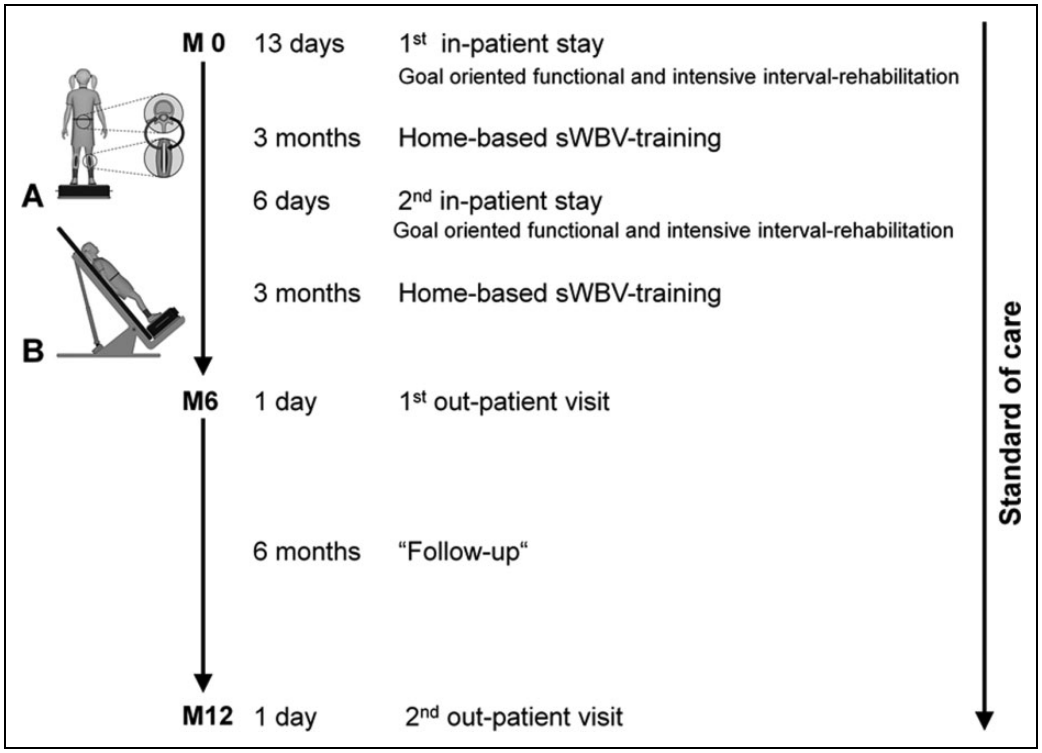

Figure 1. Cologne concept Auf die Beine—neuromuscular training based on side-alternating whole body vibration (sWBV). A, The sWBV system—spinal reflexes and muscle contractions are provoked through the side-alternating vibration stimulus. B, The sWBV system combined with a tilt table.

depicts the program *Auf die Beine*, which each of the participants completed. Baseline data were collected at the first inpatient stay (M0), after 6 months of training (M6), and after 12 months (M12, 6-month follow-up; Figure 1). If possible, the same physiotherapist assessed the child. The physiotherapists evaluating the children were not blind to the children's intervention, because all children participating in the program *Auf die Beine* receive the same intervention and all physiotherapists assessing the children also treat the children within the program. Data were collected in a secure database and retrospectively analyzed. The analysis was approved by the ethics committee of the University of Cologne (16-269) and registered at http://www.germanctr.de (DRKS00011331). Written consent for data collection and analysis was obtained from the legal guardians of all children before participation in the program *Auf die Beine*.

Table 1. Patient Characteristics at Baseline (mean [SD], or n (%)).[a]

Age, years	4.64 (1.95)
Male sex	17 (44.7%)
Height, cm	101.5 (13.1)
Weight, kg	15.8 (5.8)
BMI, kg/m^2	14.94 (2.17)
Ambulant	10 (26.3%)
Type II	28 (73.7%)
Type III	8 (21.0%)
Type IIIa	2 (5.3%)

Abbreviation: BMI, body mass index; SD, standard deviation.
[a] n = 38.

Participants

Descriptions of the sample included were children with the diagnosis spinal muscular atrophy type II and III and at least 1 of the outcome assessments completed at 2 consecutive visits. Excluded were other diagnoses influencing motor function or having surgery during the participation. Sample characteristics are depicted in Table 1.

Thirty-eight children completed the baseline visit (M0), that is, participated in the program *Auf die Beine* since March 2007 by March 2017 (Figure 2). The different outcome measures were not always available from clinical routine data (M0, M6, and M12); therefore, sample sizes vary (Figure 2). Of the 38 children, 16 children were assessed by the Gross Motor Function Measurement 66 at M0 and M6 and 14 at M12 (2 children did not return for the 12-month visit or did not have a measurement at M12). Eighteen children were assessed by the Hammersmith Functional Mobility Scale at M0 and M6 and 11 at M12 (7 children did not return for the 12-month visit or did not have a measurement at M12). Four of the 38 children with a baseline measurement (either Gross Motor Function Measurement 66 or Hammersmith Functional Mobility Scale) did not have a consecutive measurement documented and therefore were not included in the analysis.

Apparatus

A side-alternating whole body vibration system (Galileo; Novotec Medical GmbH, Pforzheim, Germany) was used to apply the vibration stimulus that provokes spinal reflexes with involuntary muscle contractions (Figure 1A).[31] Side-alternating whole body vibration applies only low forces to the body.[36] The vibration frequency is adjustable by goal setting: 5 to 12 Hz for proprioceptive training, 12 to 20 Hz for improving muscle function, and 20 to 27 Hz for increasing muscle

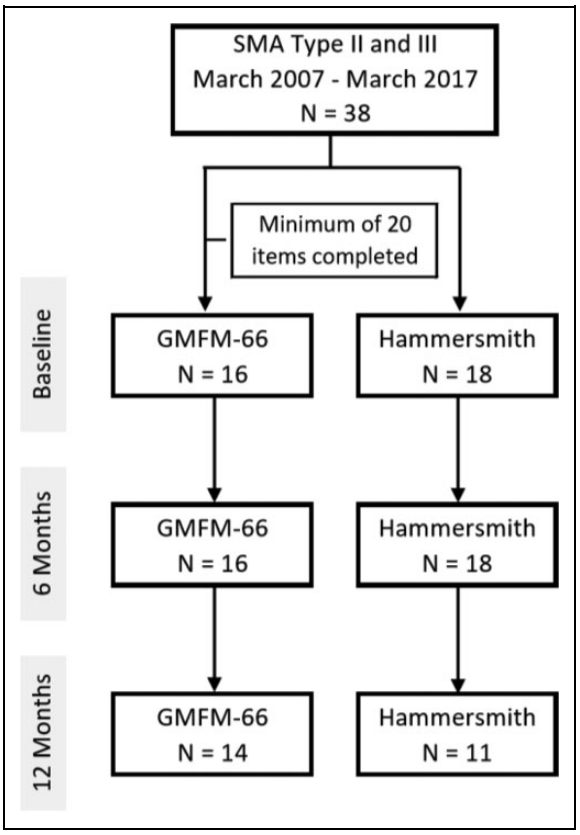

Figure 2. Flowchart sample selection and criteria.

force. The amplitude is dependent on the position of the feet on the platform between 0 and ± 3.9 mm (peak-to-peak displacement maximum 7.8 mm). Peak acceleration related to frequency is 1.57 g for 10 Hz and 9.81 g for 25 Hz. Children without standing ability use a vibrating platform combined with a tilt table (Figure 1B). The tilting angle is individually adjustable according to weight-bearing ability (0°-90°). One side-alternating whole body vibration session is 3×3 minutes long (as previously reported).[23–26,37]

Protocol

The program combines intensive, goal-directed training during 2 inpatient stays and side-alternating whole body vibration as a 6-month home training program. The first in-patient stay consists of 13 consecutive days and the second in-patient stay, done 3 months later, is 6 days duration (Figure 1). The in-patient stays consist of 4 to 5 hours of daily physiotherapy (goal-directed, high intensity, massed practice) with and without training apparatus. Children, parents, and therapists work on the child's individual goal twice a day in a functional physiotherapy setting for 1 hour. Additionally, 3 components are added: functional resistance training, pool therapy, and treadmill training with or without body weight support. Each of the additional components is applied 2 to 3 times per week.

During the first in-patient stay, the caregivers are familiarized with the side-alternating whole body vibration training protocol for home training. Vibration-assisted physiotherapy is applied 3 times daily during the in-patient stay. A side-alternating whole body vibration training device is provided for the families. The training protocol includes standardized exercises for individual goals and is applied 10 times per week for $\times$ 3 minutes during the home training. Exercises on the platform include standing (if possible with dynamic squatting), sitting, and 4-point position. Compliance with the home-based training is facilitated and monitored by a training log, which is evaluated at each visit to the rehabilitation center.

Side-alternating whole body vibration training was sometimes voluntarily continued in the follow-up period (M6-M12). This period was not part of the official program but represented parental choice.

Outcome Measures

The Gross Motor Function Measure and the Hammersmith Functional Motor Scale for spinal muscular atrophy (Hammersmith Functional Mobility Scale) were used to assess motor function. Both have been validated for spinal muscular atrophy.[38–40] Prior to 2011, we used the Gross Motor Function Measurement 66, and subsequently we used the Hammersmith Functional Mobility Scale except for very-high-functioning children. Both measurements (Gross Motor Function Measurement 66 and Hammersmith Functional Mobility Scale) were never used for the same patient at the same time.

The gross motor function measurement was designed for the assessment of gross motor skills in children with cerebral palsy,[41–43] but it contains all motor tasks typically seen in children with spinal muscular atrophy types II and III. The reliability of the Gross Motor Function Measurement 88 was tested in patients with spinal muscular atrophy.[38,44] We used the Gross Motor Function Measurement 66 because it has hierarchical structure with interval scaling; 66 basic motor function items are scored on a 4-point (0-3) scale.[42,43] The results are based upon a maximum score of 100 points. All gross motor function measurement assessments were performed without aids or orthotics. For high quality assurance, Gross Motor Function Measurement 66 scores were only calculated when a minimum of 20 items were completed (instead of 13 recommended).[43] The Gross Motor Function Measurement 66 was calculated using the Gross Motor Ability Estimator (versions 1 and 2) Scoring Software for the gross motor function measurement.

Minimal clinically important differences detect meaningful changes. Minimal clinically important differences were reported for the Gross Motor Function Measurement 66 for children ages 2 to 7 years with cerebral palsy.[45] The minimum change scores needed for a minimal clinically important differences of medium (0.5-0.8) and large (>0.8) effect size (Cohens *d*) are 2.05 points and 3.28 points, respectively, after 6 months (gray shades in Figure 3).

The Hammersmith Functional Motor Scale is the alternative disease-specific measure of motor function designed for patients with type II spinal muscular atrophy.[39] Motor skills are scored on 20 items using a 3-point (0-2) scale. The Hammersmith Functional Mobility Scale has shown good inter-rater reliability.[39,40] Mercuri et al[46] reported natural history data for the extended version of the Hammersmith Functional Mobility Scale for patients with spinal muscular atrophy types II and III and showed that 10.2% (5/49) of their nonambulant sample, below 5 years old, had changes between -2 and $+2$ points on the Hammersmith Functional Mobility Scale after 12 months. We chose the $-2/+2$ points change according to Mercuri et al., because Mercuri et al used the same time interval of 12 months, which matches our observation period. Other studies used $-3/+3$ points but had different time intervals.[10] Functional improvements and side effects were collected and documented by spontaneous parent report during M0, M6, and M12.

Data Analysis

A sample size was not calculated due to the nature of the retrospective analysis. Longitudinal differences between baseline, 6 months, and 12

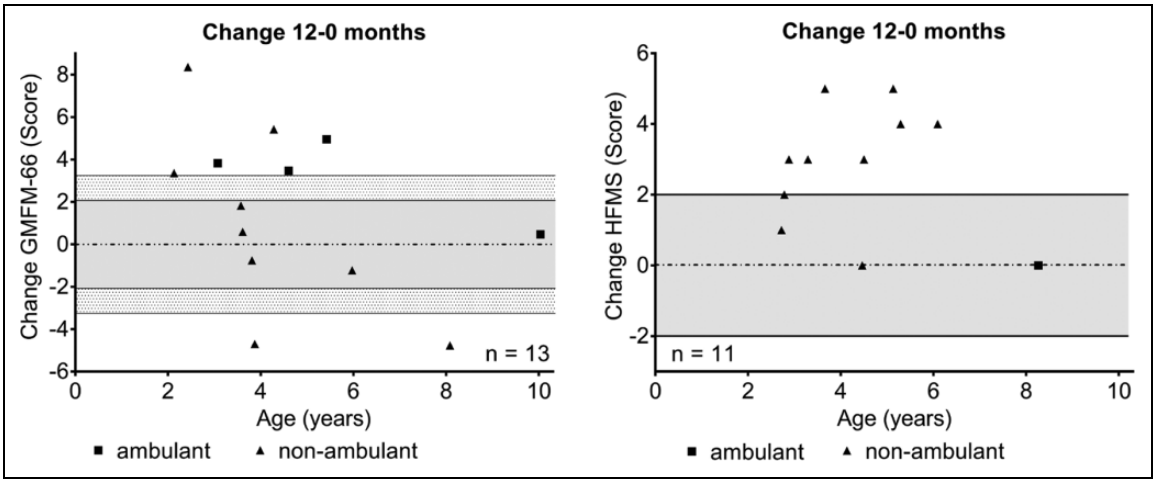

Figure 3. Individual changes at baseline (M0) to 12 months for Gross Motor Function Measure-66 (GMFM-66) and Hammersmith Functional Mobility Scale (HFMS). The GMFM-66: gray area: minimally clinically important difference (MCID) reported for children with cerebral palsy (CP) aged 2 to 7 years after 6 months.[45] Gray solid, for an MCID of medium Cohen *d* effect size (2.05 points); gray dotted: for a large Cohen *d* effect size (3.28 points). The HFMS: dotted line: ± 2 points as reported by Mercuri et al.[46] after 12 months.

Table 2. Data Summary for M0, M6, and M12.

Gross Motor Assessment	Time (months)	n	Median (IQR)	Mean (SD)	Time Difference	Δ[a]	SD (Δ)	*P* Value
GMFM-66 (Total-Score)	0	16	36.73 (31.49-50.65)	42.32 (14.84)	0-6	1.55	2.72	.044
	6	16	37.17 (33.11-50.77)	43.87 (14.56)	0-12	1.69	3.73	.124
	12	14	41.65 (31.78-56.62)	45.23 (16.91)	6-12	−0.04	3.79	.807
HFMS	0	18	17.50 (8.00-27.00)	18.00 (12.20)	0-6	1.67	2.30	.01
	6	18	19.00 (11.00-27.00)	19.67 (11.92)	0-12	2.73	1.79	.007
	12	11	20.00 (13.00-32.00)	21.00 (11.30)	6-12	1.09	2.34	.173

Abbreviations: GMFM, Gross Motor Function Measure; HFMS, Hammersmith Functional Mobility Scale; SD, standard deviation.
[a]Difference in the intraindividual means.

months were tested using Wilcoxon signed rank test because most of the data were not normally distributed. Data are presented as median and interquartile range. Means are calculated as the means of the individual differences. In order to determine the relative frequency of an increase of ≥ 2 points in the Hammersmith Functional Mobility Scale after 12 months in our patient collective compared to that of Mercuri et al, the exact binomial test was used. Presented *P* values are 2 sided and considered as statistically significant if $P < .05$. Data were analyzed using SPSS Statistics version 23 (IBM Corp, Armonk, New York).

Results

Gross Motor Function Measurement 66 data were available for 16 patients during the active phase (M0-M6) and 14 at follow-up (M12; Figure 2). The Gross Motor Function Measurement 66 showed an increase of $1.69 - 3.73$ ($P = .124$) points after 12 months (Table 2). The Hammersmith Functional Mobility Scale was available for 18 patients (M0-M6) and for 11 until M12 and showed a significant increase after 12 months of 2.73 ± 1.79 points ($P = .007$). After 6 months, significant improvement could be seen in both groups. The individual changes from M0 to M12 for the Gross Motor Function Measurement 66 and the Hammersmith Functional Mobility Scale are depicted in Figure 3 for ambulant and nonambulant children, considering the minimal clinically important differences reported for children with CP[45] and ± 2 points for the Hammersmith Functional Mobility Scale.[46]

Eight of 11 patients in the Hammersmith Functional Mobility Scale group showed an increase of ≥ 2 points after 12 months; 4 children showed an increase between 0 and 2 points. The relative frequency for a Hammersmith Functional Mobility Scale score of ≥ 2 points after 12 months was 72.7% (8/11). Mercuri et al showed a relative frequency for an increase of ≥ 2 points in their nonambulant sample below 5 years of age after 12 months of 10.2% (5/49). The difference between the samples is significant ($P < .001$).

Functional improvements reported by the parents are shown in Table 3. Of the 14 patients in the Gross Motor Function Measurement 66 group (follow-up, M12), 2 patients continued training and 5 in the Hammersmith Functional Mobility Scale group ($n = 11$ in M12). Training intensities ranged between 2×2, 4×2, 5×2, 4×1, 6×1, and 7×1 training units (3 minutes) per week. Parents of 3 children reported adverse events as shown in Table 4, which were interpreted as not likely attributable to the program.

Table 3. Parent Report for Improvement as Documented in the Patient File at M0, M6, M12 (Multiple Events per Child Possible).

Parent Report on Individual Improvement	M[a]	N[b]
General stability/trunk stability, head control, balance, coordination	6	17
	12	9
Self-motivation, activity, independence, self-confidence	6	7
	12	3
Endurance, general power	6	4
	12	3
Movement transitions	6	2
	12	1
Less infections/better recovery	6	3
	12	2
Less prone to falling	6	5
	12	2
Physical therapy (local)	6	2
Arm function	6	3
Activity radius improved in sitting	6	1
Better activity of the feet	6	1
Standing with assistance	6	1
Climbing stairs	6	1
Is able to swim	6	2
Ride bicycle without training wheels	6	1
More activity in wheelchair	6	1
Rarely uses wheelchair anymore	6	1
Less "shaking"	12	1
Scoliosis (better)	12	1

[a]M = month (M6, M12).
[b]N = number of events.

Table 4. Parent Report for Deterioration as Documented in the Patient File at M0, M6, M12.

Parent Report on Individual Deterioration	Child	M[a]	Voluntary sWBV M6-12	Rating	Relation to the Program
Hand function	1	M12	No	Nonserious	No
Spine deformation	2	M12	Yes	Nonserious	No
Hand function		M12	Yes	Nonserious	No
Spine deformation	3	M12	Yes	Nonserious	No
Knee contracture		M12	Yes	Nonserious	No

[a]M = month (M6, 12).

Discussion

The results of our uncontrolled retrospective observation of the neuromuscular treatment program *Auf die Beine* combining intensive, goal-directed training during 2 in-patient stays and side-alternating whole body vibration as a 6-month home-training program indicate significant improvement in mobility measured by the Hammersmith Functional Mobility Scale after 12 months in 11 children with spinal muscular atrophy types II and III, with a relative frequency for an Hammersmith Functional Mobility Scale score of $\geq$2 points of 72.7% (8/11). In comparison, only 10.2% (5/49) showed changes beyond 2 points at this age in natural history.[46] Phase 3 clinical trial addressing the efficacy of nusinersen in the age-group 2 to 6 years[10] found an increase of more than 3 points in the untreated group of 26.3% (7/11). The difference between our and Mercuri's[10] sham sample is significant ($P < .010$). Similar results have been reported in the nusinersen trial. The nusinersen intervention group showed an improvement of more than 3 points in 56.8% ($P = .226$ compared to our sample). However, our changes could also be related to typical development, one (or more than one) of the applied therapies, or other unmeasured variables.

A similar pattern could be observed for the Gross Motor Function Measurement 66: 6 of 13 children improved beyond the minimal clinical relevance for a medium Cohen *d* effect size.[45] To our knowledge, minimal clinically important differences are not reported for patients with spinal muscular atrophy for the gross motor function measurement; therefore, we used the values for CP.

We observed nonsignificant but further improvement in the Gross Motor Function Measurement 66 and Hammersmith Functional Mobility Scale after the intensive training period. Neuromuscular training with side-alternating whole body vibration has the advantage of utilizing the monosynaptic reflex through mechanical stimulation. In patients with spinal muscular atrophy, the muscle is primarily "healthy" but does not receive enough efferent innervation. Therefore, the patients experience secondary muscle atrophy and deterioration of muscle strength, which have additional negative effects on the skeletal system (eg, contractures and decreased bone mineral density).[47,48] The importance of muscular (afferent) information on the neuronal system has been described.[49–51] Further improvement after active training (M6) can indicate better mobility in daily living and permanent repetition of the neuromuscular circuit once a better mobility level has been established after intensive training.

None of the children who trained unsupervised between M6 and M12 deteriorated significantly in motor function. However, most of the parent-reported deteriorations were reported in this group. These events are possibly not related to the program *Auf die Beine* but possibly to the "unsupervised" training between M6 and M12. Therefore, we recommend controlled training within a structured and supervised concept.

Study Limitations

This study is limited by the description of a multimodular physiotherapy program. It is not possible to asses which intervention was the most contributory. The patients were a heterogeneous group with different levels of mobility and there was also a lack of a control group. It has to be considered that our sample was young, and at this age, natural development can still be expected. However, early deterioration can be expected as well.[46] It also has to be taken into account that Mercuri et al used the extended version of the Hammersmith Functional Mobility Scale for the natural history cohort and we used the 20-item version; therefore, results must be interpreted with caution. Due to the nature of this retrospective analysis of a routine procedure, we do not have data on observer reliability.

Future studies should include new developments in motor assessment for patients with spinal muscular atrophy, such as the Motor Function Measure-32 and the extended and revised version of the Hammersmith Functional Mobility Scale.[52–54] The results include unsupervised home-based side-alternating whole body vibration training; this should also be investigated in the future. Future research should further investigate the encouraging trends shown in the results reported, specifically the combination of pharmacological and rehabilitative approaches. Timing of treatment and intensity of muscle activation (depending on duration of medical treatment) have to be analyzed in controlled trials.

Conclusion

The Cologne neuromuscular training program *Auf die Beine* was safe in patients with types II and III spinal muscular atrophy. The results describe significant beneficial changes measured by the Hammersmith Functional Mobility Scale after 12 months through home-based side-alternating whole body vibration exercises combined with goal-oriented functional and intensive interval rehabilitation. Whether this actually leads to long-term clinical benefit shall be investigated in further studies.

Authors' Note

This project is part of the Global Pediatric Leadership Program of Harvard Medical School and has been reviewed by Phillip L. Pearl. All authors fulfill the 4 criteria for authorship recommended by ICJME and all who meet the 4 criteria are identified as authors. Further information can be requested by the corresponding author (CS).

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Author Contributions

C. Stark contributed to conception and design; acquisition, analysis, and interpretation; drafted the manuscript; and gave final approval. I. Duran contributed to conception and design. acquisition, analysis, and interpretation; critically revised the manuscript; and gave final approval. S. Cirak contributed to interpretation; critically revised the manuscript; and gave final approval. S. Hamacher contributed to analysis and interpretation; critically revised the manuscript; and gave final approval. H. K. Hoyer-Kuhn contributed to conception and design; contributed to interpretation; critically revised the manuscript; and gave final approval. O. Semler contributed to conception and design; critically revised the manuscript; and gave final approval. E. Schoenau contributed to conception and design; contributed to interpretation; critically revised the manuscript; and gave final approval. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Eckhard Schoenau is medical director of the UniReha GmbH and Ibrahim Duran is employed by UniReha GmbH.

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Ethical Approval

This study was approved by the ethics committee of the University of Cologne, Germany.

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