Safety and Effectiveness of Progressive Moderate-to-Vigorous Intensity Elastic Resistance Training on Physical Function and Pain in People With Hemophilia

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Objective. Strength training is recommended for people with hemophilia; however, published data are anecdotal and have methodological limitations. The purpose of this study was to evaluate safety and effectiveness of progressive moderate-to-vigorous intensity elastic resistance training on physical function and pain in this patient population.

Methods. A randomized controlled trial was conducted in a university laboratory setting, where 20 patients (17 with severe, 1 with moderate, and 2 with mild hemophilia) who were aged 21 to 53 years received evaluations at baseline and 8-week follow-up. Participants were allocated to intervention (progressive

strength training) or control (usual daily activities) groups. The intervention group trained 2 days per week during 8 weeks with elastic resistance. Intensity during the first 2 weeks was a 20-repetition maximum (RM) and increased progressively toward 15RM, 12RM, and finally 10RM. The primary outcome was muscle strength. Secondary outcomes were: Timed “Up and Go” Test (TUG), sit-to-stand, ROM, Haemophilia Joint Health Score (HJHS), kinesiophobia score, global impression of pain change, general self-rated health status, and desire to exercise.

Results. The intervention group showed greater strength improvements than the control group in almost all of the joints, with moderate to high effect sizes. The intervention group also showed better TUG and sit-to-stand scores than the control group (moderate effect size), greater ROM at the knee flexion with the right leg (trivial effect size), and better HJHS at the left knee (small effect size). The intervention group showed greater overall pain reduction, self-rated overall status, and desire to exercise than the control group.

Conclusions. Progressive strength training with elastic resistance performed twice a week during 8 weeks is safe and effective in people with hemophilia to improve muscle strength and functional capacity, reduce general pain, and improve self-rated health status and desire to exercise.

Impact. This study provides evidence for the use of a specific strength training regimen for people with hemophilia.

Lay summary. People with hemophilia of differing levels of severity, with adequate coverage with clotting factor, can safely engage in progressive strength training and can improve their functioning.

Hemophilia is a hereditary bleeding disorder caused by deficiencies in coagulation factors VIII (hemophilia A) and IX (hemophilia B).[1] This disease produces spontaneous bleeding episodes, especially at intra-articular level,[2] initiating a vicious cycle of pain,[3] physical inactivity, muscle weakness, muscle atrophy and increased bleeding risk.[4] In consequence, synovitis and cartilage and bone deterioration occur[5] leading to joint disease in 90% of people with severe hemophilia.[6]

Avoided in the past, physical exercise is now recommended in people with hemophilia with adequate coverage factor. Among different types of exercise, strength training is advised to recover physical function in those with chronic arthropathy,[7] becoming more important with age[8] and arthropathy severity.[9] Strength training can decrease the number of circulating inflammatory cells, reducing or preventing bleedings and associated pain.[10]

Although recent reviews[7] and expert opinions[11] highlighted the relevance of strength training for people with hemophilia, published data remains anecdotal and with methodological limitations. Thus, it remains unclear whether strength training can improve physical function and reduce pain among adult people with hemophilia. Several previous studies lacked clear reporting of exercise dosing and progression, and when reported, low intensities and volume usually prevail. As with dosing of medicine, sufficient exercise volume (ie, quantity) and intensity (ie, magnitude of the dose) are needed to induce proper morphological and neural adaptations.[12] While low intensities (eg, 30% of one-repetition maximum) can improve muscular endurance or even maximal strength gains in untrained individuals, higher intensities (eg, 80% of one-repetition maximum) are superior to elicit muscle strength and neural

adaptations.[13] In the same vein, to induce muscle hypertrophy with low intensities, repetitions need to be performed with sufficient fatigue (ie, until muscle failure or near muscle failure) to stimulate the motor units with highest threshold[14] and enhance skeletal muscle protein synthesis.[15]

In previous studies, it is plausible that fear of producing bleedings and pain hindered investigations on high-intensity strength training among people with hemophilia. However, with inclusion of adequate coverage factor, strength training studies are needed to find more optimal dosing in terms of effectiveness and safety. In this sense, progressive strength training, which has showed effectiveness in treating other musculoskeletal conditions[16] could be optimal in people with hemophilia due to the gradual intensity increase. In addition, besides careful supervision and a correct exercise technique, equipment can be a relevant choice to minimize injury risk in people with hemophilia. Exercise programs based on elastic resistance bands are especially interesting due to minimal impact forces and low risk of accidents compared with traditional heavy weights.[17] However, there are no studies applying progressive moderate-vigorous intensity strength training with elastic resistance in people with hemophilia.

The purpose of the present study was to evaluate safety and effectiveness of progressive moderate-vigorous elastic resistance training on physical function and pain in people with hemophilia. We hypothesized that the program would be safe and effective in increasing muscle strength and functional capacity while reducing pain.

[H1] Methods

[H2] *Participants*

The present study was a randomized controlled trial with two parallel groups. Subjects between 18-60 years old, diagnosed with Hemophilia and visiting a local hospital (University and Polytechnic Hospital La Fe, Valencia, Spain) due to an appointment at the Haemostasis and Thrombosis Unit during 2017 were candidates for the present study and invited to participate. Key inclusion criteria were: 1) diagnosis of mild, moderate or severe Hemophilia A or B; 2) severe subjects receiving prophylactic treatment; 3) willingness to exercise twice a week during the training program and to complete the pre- and post-program evaluations; 3) approval by their hematologist to participate in the exercise program; 4) informed consent signed. Key exclusion criteria were: 1) the inability to attend exercise sessions at least twice a week for 8 consecutive weeks; 2) non-adherence to instruction on proper exercise technique; 3) joint replacement in the previous year or surgical procedures performed 6 weeks prior to or during the exercise program; 4) participation in any other form of programed strength exercise during the intervention period; 5) changes in medication during the study; and 6) joint or muscle bleeding in the last 3 months; 7) detectable FVIII inhibitors at screening (titer ≥ 0.4 Bethesda unit); 8) another hemostatic defect; 9) need for major surgery (10), or withdrawal of informed consent.

All participants were informed about the purpose and content of the project and gave their written informed consent to participate in the study. All procedures described in this section were approved by the institution's review board (H1461147538087) and comply with the requirements listed in the 1975 Declaration of Helsinki and its amendment in 2008. The study was registered in ClinicalTrials.gov (NCT02781233) and reporting adheres to the CONSORT.

[H2] *Randomization and allocation*

After receiving a list with possible subjects from a medical doctor (neither involved in the testing nor training sessions), the main researcher involved in the recruitment process approached the participants, explained them about the study, and asked if they would be willing to participate. Those agreeing (20 subjects), were randomly allocated following simple randomization procedures (computerized random numbers), with an allocation ratio of 1:1 to either an intervention group (progressive training) or control (usual daily activities). This allocation process was performed by a person who was not involved in the testing and training sessions, and did not have access to the results of these test and training data.

[H2] *Intervention*

The intervention consisted of a group-based training program for two days per week for a total of 8 weeks, especially focused on increasing muscle strength in the knee-, elbow- and ankle-joints (Figure). Table 1 shows the complete intervention training program. Sessions were performed at the same time of the day at the university and were separated by 72hours. The severe subjects had their prophylactic treatment 1-26 hours before each training session. Sessions took place under the supervision of two physical therapists and a sport scientist and Strength & Conditioning Specialist.

[H2] *Control group*

The control group performed usual daily activities during 8 weeks. During the study period, all the participants were asked to maintain their normal diet and usual exercise practices, avoiding additional changes that could influence the results.

[H2] *Outcome measures*

The following variables were collected from the medical record by a secondary person: age, type and severity of hemophilia, prophylaxis regimen (weekly coagulation factor dose), Annual Bleeding Joint Rate (ie, bleeding episodes during the last 12 months, before starting the study) and degree of hemophilic arthropathy measured radiologically with the Pettersson score. This scale evaluates the different elements of the articular alteration using an additive score of 0-13 per joint, being 0 the normality and 13, maximum joint alteration.[18] Pharmacokinetics were determined using Bayesian post hoc estimation of individualized pharmacokinetics values (half-life (t1/2), peak level and level at training session), obtained using the Web Accessible Population Pharmacokinetic Service for Hemophilia (WAPPS-Hemo tool).[19]

Participants were scheduled for two testing days, baseline and after eight weeks. All measurements were performed at the university by the same two physical therapists, who had previous experience with the tests, were blinded to group allocation and were not involved in the training supervision to avoid possible risk of bias.

During baseline testing, height (IP0955, Invicta Plastics Limited, Leicester, England) and weight (Tanita model BF- 350, Tokyo, Japan) were firstly recorded as descriptive data. In addition, the following variables were assessed at baseline and after the intervention: the primary outcome was between-group difference in muscle strength gains. Isometric knee flexion and extension, isometric ankle plantarflexion and dorsiflexion and isometric elbow flexion and extension were assessed with a portable hand-held dynamometer (Nicholas Manual Muscle Tester, Lafayette Instruments, Indiana, USA) with tests performed against fixed resistance. These joints were selected

since are the most affected in people with hemophilia.[1] These Specifically, for the knee extension and flexion, subjects were seated with back support, with knee angle of 70° and hip angle of 110°. For measuring the isometric knee extension strength, the dynamometer was positioned perpendicular to the axis of the tibia, proximal to the ankle, and fixated by a belt anchored to a handlebar. For measuring the isometric knee flexion strength, the dynamometer was placed on the posterior aspect of the lower leg, and fixated by a belt anchored to a handlebar. Hand-held dynamometer testing has shown good-excellent intra-rater reliability for knee flexors, with an intraclass correlation coefficient (ICC) range of 0.76-0.94 and excellent (ICC range of 0.92-0.97) for knee extensors.[20] For ankle dorsiflexion and plantarflexion, subjects were positioned in long sitting (hips flexed and knees extended), with a backrest and the ankle in a neutral position according to a previous standardized procedure that demonstrated high reliability, with ICCs ranging from 0.88 to 0.90 and 0.94 to 0.96 respectively.[21] For ankle plantarflexion, the dynamometer was fixated with a belt anchored to a wall bar and positioned against the plantar surface of the foot, just proximal to the metatarsal heads; and for ankle dorsiflexion, against the dorsal surface of the foot, just proximal to the metatarsal heads. For the elbow flexion and extension tests, subjects were with elbows at 90° in a seated position with erect posture, no back support and with both feet placed flat on the floor, with force being exerted against a fixed table. Isometric elbow flexion and extension strength tests with the hand-held dynamometer have demonstrated good-excellent reliability, with ICCs of 0.87 and 0.88-0.92, respectively.[22]

Passive ROM was measured at the aforementioned joints, with a universal goniometer (Absolute Axis goniometer, Baseline evaluation instruments, White Plains, USA) in

accordance with the Haemophlia Joint Health Score 2.1 (HJHS 2.1) recommendations. The HJHS and the Tampa Scale for kinesiophobia (TSK-11) were used to evaluate joint health and fear of movement beliefs respectively, with higher scores reflecting worse condition. Both measures have shown high test-retest reliability values, with an ICC of 0.89 for the HJHS[23] and a Cronbach's α of 0.80 for the TSK-11 total score.[24]

The Timed Up and Go (TUG) and the sit-to-stand test were used to measure functional capacity.[25] The TUG measures the time that a person takes to rise from a standard armchair (not using their arms to stand up), walk to a line on the floor 3 m away, turn around, walk back to the chair and sit down again. The TUG has excellent intrarater reliability, with an ICC of 0.94.[26] The sit-to-stand test measures the time taken to stand up and sit down from a standard chair with arms three times, as quickly as possible.[27] The sit-to-stand test has demonstrated excellent intrarater reliability, with an ICC of 0.89.[28] In both functional capacity tests, the time is measured in seconds with a chronometer, with shorter times indicating better performance. The highest value of 2 trials for each of these tests was used for the analysis.

In addition, the following perceived changes were assessed only after the intervention: the patient global impression of pain change was evaluated by asking the following question: "Since the start of the study, my overall pain status is": 1) very much improved, 2) much improved, 3) minimally improved, 4) no change, 5) minimally worse, 6) much worse, and 7) very much worse. The patient global impression of change is a valid tool and represents a true meaningful change to the person,[29] being strongly associated with pain intensity, regardless of the pain cause, intervention, or

participant characteristics like gender or age.[30] A previous study found high test-retest reliability when using a global rating of change scale, with an ICC of 0.90.[31]

Finally, general health status and desire of practicing exercise were evaluated on a 3-point scale of "worsened", "unchanged", or "improved". Finally, participants were asked to inform if any adverse event occurred during the duration of the study (bleedings, pain exacerbation). Similar three-point scales have been traditionally used to self-rate health status or other outcomes[32,33] and have showed a good reliability, with a coefficient of 0.89.[34]

[H2] *Sample size*

An a priori power analysis was conducted in G*Power (3.1.9.2 version) software to calculate the required sample size, using a previous research as reference. In the study of Mulvany et al,[35] a medium effect size (d=0.7) was obtained in the isometric knee strength outcome. Therefore, with the present study design, accepting a 5% alpha risk (α=0.05) and 20% beta risk (β=0.2; power=0.80), a total of 20 subjects were required to detect at least a medium effect size (*f*=0.35; d=0.7).

[H2] *Statistical analyses*

Descriptive data of subjects at baseline were compared using the unpaired t test. The change-score from baseline to follow-up between intervention and control were evaluated using linear mixed models (Proc Mixed, SAS version 9.4) according to the intention-to-treat principle. Subject was entered as random effect and fixed effects were 1) group, 2) the baseline value of the outcome variable. The estimation method was restricted maximum likelihood with degrees of freedom based on the Satterwaite approximation. Outcomes are reported both as within-group changes from baseline to

follow-up and between-group differences from baseline to follow-up, with the latter being the comparison between control and intervention. Changes were controlled for the baseline value of the outcome as a covariant. The covariance structure was set to variance component. P-values less than 0.05 were accepted as statistically significant. Effect size (Cohen´s d) was calculated and described as: <0.2= trivial effect; 0.2= small; 0.5= moderate; 0.8= large. Minimal clinically important differences were calculated according to previous recommendations[36] by multiplying pooled baseline standard deviation scores by 0.2.

[H2] ROLE OF THE FUNDING SOURCE: The funders played no role in the design, conduct, or reporting of the study.

[H1] Results

The Supplementary Figure shows the complete flow chart diagram of the study progress. Table 2 shows complete demographic and descriptive data. Participants had no previous experience with elastic resistance training.

The severe subject with daily prophylactic factor had a coverage level at training time of 37.8 IU/dL. The mild subject had a coverage level at training time of 11.0 IU/dL (basal level). The other subjects at the intervention group had a coverage level at training time during the first weekly session of 58.0 (SD 17.2) IU/dL, while at the second weekly session they had a coverage level of 10.0 (SD 4.6) IU/dL.

All subjects attended all the sessions. Tables 3 and 4 show primary and secondary outcomes results. No adverse events (eg, bleedings) or kinesiophobia changes were

reported. At follow-up, the intervention group showed greater muscle strength in almost all the joints (moderate-high effect sizes) and better TUG and sit-to-stand (moderate effect size) than controls. In addition, the intervention group showed greater ROM at the knee flexion with the right leg (trivial effect size) and better HJHS at the left knee (small effect size) at follow-up. All the significant between-group differences at follow-up were clinically important, except at the HJHS and ROM.

Table 5 shows complete perceived changes data. The intervention group showed a significantly greater overall pain reduction ($p=0.037$), self-rated overall status ($p<0.001$) and desire to exercise ($p<0.001$) than the control group.

[H1] Discussion

The main findings of the present study are the safety and effectiveness of progressive strength training in improving physical function and reducing general pain in people with hemophilia.

The high exercise intensity and volume used in the current study likely explain the strength gains achieved by the intervention group. These adaptations occurred in spite of a relatively low training frequency. With the duration of our program, muscle strength gains are primarily mediated by adaptations in motor unit recruitment and rate coding[37] and secondarily by muscle hypertrophy. In fact, changes in muscle size and fascicle angle (which could be reduced due to a arthropathy) are moderately associated with isometric strength improvements.[38] Besides these anatomical and neuromuscular factors, many other factors exist that can influence strength gains after a training program. In fact, a very large variation (from −8 to 60%) has been observed in strength gains during the leg press among untrained healthy subjects.[39]

Interestingly, the influence of age in strength gains remains less clear and seems to be muscle-dependent. For instance, while the previous study found that age did not affect strength gains,[39] another recent study[40] found that average plantarflexion strength gains changed little with increased age in healthy individuals. By contrast, dorsiflexion strength was more affected by this factor, with an absence of strength gains among elderly subjects. Interestingly, dorsiflexion strength was the least affected strength test after our intervention. We only found two cases where muscle strength was only increased in one side (knee flexion left and elbow flexion right). While a study found that limb dominance may provide greater elbow and knee muscle strength in healthy young subjects,[41] more recent studies have found disparity when using other muscles[42] or among females.[43] Another more relevant factor influencing strength gains in people with hemophilia could be the joint health status, since a worse condition is associated with a weaker extremity.[44] Thus, it is plausible that those having a greater degree of hemophilic arthropathy would have a reduced baseline strength performance, having a greater window of opportunity for improving. However, no previous studies exist aiming at explaining the influence of such factors on strength changes after an intervention in people with hemophilia. Thus, future studies investigating this should be conducted.

The intervention group showed greater strength improvements than controls in almost all the measured joints, with especially remarkable changes at the knee extension. In contrast, a previous study in people with hemophilia found no quadriceps strength improvements after a walking, balance and low intensity strength training performed 5-7 days/week during 4 months.[45] However, in line with our results, other studies in people with hemophilia found increased strength after a 6-week program including

stretching, cardiovascular and strength training,[35] 6 months of proprioceptive and low intensity strength training[46] or a 6-month mobility, coordination, strength and endurance training.[47] In previous studies, the absence of control group[35] or the use of participants without Hemophilia as controls[46] are clear limitations. Interestingly, two of these studies included elastic resistance, albeit intensity prescription was based on the colors of the band[35] or was not reported,[46] hindering comparison across studies and proper individualized dosing.

Regarding the secondary outcomes, TUG and sit-to-stand showed greater improvements in the intervention group, with a moderate effect size. A previous study found that walking performance in boys with Hemophilia may depend on knee extensor strength.[48] In the same vein, knee extensor strength has been highlighted as the key determinant of TUG in subjects with knee osteoarthritis.[49] Supporting this notion, a previous program in people with hemophilia[45] that failed in improving knee extensor strength did not find changes at the TUG, sit-to-stand test and also at gait speed test while other studies reporting muscle strength gains showed greater walking performance.[35,47]

ROM only significantly improved after the intervention in the knee flexion with the right leg, although with a non-clinically relevant difference. Interestingly, ROM at the knee flexion with the left leg and the elbow flexion with the right arm showed a borderline significant result favoring the intervention group, with a small effect size and clinically important differences. A previous non-controlled trial[35] including prolonged flexibility and strength exercises did increase knee, ankle and elbow ROM. Despite being plausible that by adding specific flexibility exercises we could have found

greater ROM gains, our findings are somehow positive, showing some improvement after only performing strength training. ROM results could be influenced by muscle strength gains[50] or pain reduction. Finally, a relatively small opportunity window for ROM improvement must be considered due to the arthropathy degree of some subjects**,** as Petersson scores reflect, especially in ankles, with average values of 6.1 and 5.9 in right and left ankle, respectively, in the intervention group.

Joint health measured with the HJHS improved in the left knee after the intervention and this probably caused a borderline significant result at the total score favoring this group, with a small effect size and a clinically relevant difference. Unfortunately, no longitudinal studies evaluated responsiveness of the HJHS and its sensitivity for assessing progression in adult subjects with more severe joint damage is likely limited.[51] However, this test is associated with bleeding rates and physician global assessment of joint health[51] so our results for this outcome could have clinical implications.

The intervention group showed greater overall pain reduction and self-rated overall health status after finishing the study than the control group. Importantly, 70% of our participants reported a clinically important pain change, defined in a previous study[30] as 'much improved' or 'very much improved', which related to approximately 30% pain reduction regardless of study, disease type, age, sex, study result, or treatment group. Together with the high prevalence of constrains to perform daily life activities due to pain in adult people with hemophilia,[52] our results seem relevant. A mechanism explaining the improvement of this outcome is the release of peripheral and central beta-endorphins, linked with pain sensitivity changes.[53] Previous RCTs showed no clear

pain reduction after an educational physiotherapy program that included home-based low-intensity isometric exercise,[54] after a home-based body weight strength and balance training[55] or after mobility, coordination, strength and endurance training.[56] However, the later study[56] found an improved general health perception after the program, in line with our results. Both the overall pain and physical function changes in the intervention group could have mediated the improved self-reported health status.

The intervention group increased the desire of practicing exercise after the program, while 90% of controls did not change. This psychological benefit may be caused by the general positive effects of the program and could explain its high adherence. Despite no other similar studies explored this outcome in people with hemophilia, a previous strength training program[32] demonstrated improving the desire to exercise in most of the participants when the program was group-based and supervised. Proper guidance and keeping in touch with others peers are key elements to participate in weekly group-based programs.[57] This could also be more relevant in people with hemophilia due to their possible safety concerns about strength training.

A novel and relevant finding is that people with hemophilia in the intervention group tolerated a strength training program with higher intensities and volume than previously reported in the literature, without any bleeding or other adverse event, or without increased fear of movement. An expert consensus statement recommended that plasma factor level should be between 15 to 30% when intensive sport activity is carried out.[58] However, most of the severe subjects in our intervention group (90% of participants) were below these levels during the second weekly session. Specifically, that session was performed 24 to 26 hours after the last prophylaxis infusion, with

coverage of factor VIII lower than 15% -although near. Some factors that could explain the safety of our program are the close supervision, progressive intensity without reaching muscle failure and exercises performed with controlled speed. In fact, we have previously showed the general good tolerability and safety of some of these exercises when performed in a single session.[59,60] In addition, the term "intensive" needs to be better defined since depend on many factors. Interestingly, weight-training sports have demonstrated relatively low injury rates compared with common team sports.[61] It seems that when performed with adequate coverage factor, strength training of sufficient high intensity and volume can be safely performed to achieve positive physiological adaptations. To our knowledge, this is the first study providing specific factor coverage data during a strength training intervention. Future studies should make an attempt to provide this data so exercise prescription in this population can be improved.

An increased kinesiophobia in people with hemophilia would affect adherence and initiates a vicious cycle of physical inactivity to avoid pain, increasing muscle weakness, disability and depression probability,[62] which in turn leads to chronic pain and greater bleeding risk[63] likely accelerating arthropathy severity. It is plausible that the low levels of kinesiophobia showed by our participants before starting the study explain the absence of reduction. In addition, multidisciplinary programs combining physical training and education seem more effective in reducing kinesiophobia, at least in subjects with chronic pain.[64] Unfortunately, no other intervention studies have evaluated kinesiophobia changes in people with hemophilia.

[H2] *Study limitations*

The generalizability of our results could be improved with a larger sample size. However, the number of participants was sufficient in accordance with an a priori power analysis. Since neuromuscular adaptations have a training-specific component, a possible limitation of our study is that dynamic muscle strength rather than isometric assessment could have provided further differences. However, isometric assessments with a hand-held dynamometer are valid and reliable.

Together with the novelty, the exercise dosing and clear reporting of our program are major strengths of the current study. A more detailed documentation of training protocols is needed in future studies, allowing subjects and researchers understanding what was done and what caused the specific results.

[H1] Conclusions

Progressive moderate-vigorous intensity strength training with elastic resistance performed twice a week during 8 weeks is safe and effective in people with hemophilia to improve muscle strength and functional capacity, reduce general pain and improve self-rated health status and desire to exercise.

Author Contributions and Acknowledgments

Concept / idea / research design: J. Calatayud, S. Pérez-Alenda, C. Cruz-Montecinos, L.L. Andersen, J. Casaña

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The authors gratefully thank the contribution of the participants.

Ethics Approval

This study was approved by the University of Valencia review board (H1461147538087) and complies with the requirements listed in the 1975 Declaration of Helsinki and its 2008 amendment.

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Clinical Trial Registration

This study was registered in ClinialTrials.gov (NCT02781233).

Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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Table 1. Intervention Training Program.[a]

Frequency	2 days per week during 8 weeks.
Exercises	Knee extension, knee flexion, ankle plantarflexion, ankle dorsal flexion, elbow flexion, elbow extension, shoulder abduction and hip abduction, all performed with full range of motion (ROM) and with elastic bands (TheraBand CLX, The Hygenic Corporation, Akron, OH, USA).
Exercise order	In each session, the exercises were performed in a different order and in a rotation manner, switching from one exercise to the next so that the muscles were fatigued alternately.
Warm-up	A warm-up set was performed before each specific exercise by using a light resistance to easily perform 10 repetitions without fatigue.
Volume	3 sets of each exercise. The number of reps decreased as intensity increased.
Rest	1 minute between sets and exercises.
Intensity	Intensity progressively increased to gradually augment the stimulation during the intervention, starting with a moderate intensity of 20 repetition maximum (RM) and increasing each two weeks towards high intensities of 15RM, 12RM and finally 10RM. Subjects were asked to complete the targeted number of repetitions (eg, 20) with an elastic tension that would allow performing an additional repetition (eg, 21) once they stopped the exercise -that is, finishing the set staying one repetition below muscle failure. To achieve adequate exercise intensity during each exercise, the elastic bands were pre stretched to approx. 50% of the initial length (initial length, 1.9 m) and then different bands were added when needed to reach the desirable intensity. With this purpose, red, blue, black, silver and gold elastic band colors were allowed, alone or in combination.
Velocity	Moderate lifting velocity (approximately 1 second concentric and 1 second eccentric).

[a]RM = repetition maximum; ROM = range of motion.

Table 2. Descriptive Data of Subjects at Baseline.[a]

	Control (n = 10)		Intervention (n = 10)		*P* (95% CI)
	Mean	SD	Mean	SD	
Demographics and pharmacokinetics					
Age (years)	39.1	8.4	36.3	10.5	.52 (-11.76 to 6.16)
Height (cm)	174.3	7.6	172.8	7.9	.67 (-8.80 to 5.80)
Body mass (Kg)	83.1	27.5	81.7	21.7	.90 (-24.66 to 21.86)
HIV (positive/negative)	4/6		4/6		-
HCV (positive/negative)	5/5		6/4		-
Type of hemophilia (A/B)	8/2		10/0		-
Severity of hemophilia (severe/moderate/mild)	8/1/1		9/0/1		-
Replacement treatment (prophylaxis/on demand)	8/2		9/1		-
FVIII dose (IU/Kg) (n = 9 intervention; n = 6 control)	27.1	9.4	29.6	13.9	.69 (-10.65 to 15.68)
FIX dose (IU/Kg) (n = 0 intervention; n = 2 control)	48.5	10.5	-	-	-
FVIII peak (n = 9 intervention; n = 6 control)	75.8	25.2	53.6	17.3	**.049** (-44.39 to -0.08)
FIX peak (n = 0 intervention; n = 2 control)	47.6	4.7	-	-	-
FVIII $t_{1/2}$ (h) (n = 9 intervention; n = 6 control)	15.8	3.7	12.4	4.3	.10 (-7.65 to 0.69)
FIX $t_{1/2}$ (h) (n = 0 intervention; n = 2 control)	28.4	0.2	-	-	-
Musculoskeletal data					
Total knee replacement (yes/no)	0/10		1/9		-
Total ankle replacement (yes/no)	1/9		0/10		-
ABJR	1.2	1.2	0.7	0.8	.30 (-1.48 to 0.48)
HJHS right elbow	4.4	3.6	5.4	6.2	.67 (-3.86 to 5.86)
HJHS left elbow	2.2	2.9	5.5	5.2	.10 (-0.74 to 7.34)
HJHS right knee	2.8	4.6	3.6	5.4	.73 (-3.92 to 5.52)
HJHS left knee	2.4	3.9	3.4	6.1	.67 (-3.79 to 5.79)
HJHS right ankle	5.9	4.3	4.9	2.7	.54 (-4.40 to 2.40)
HJHS left ankle	5.3	2.8	5.4	3.9	.95 (-3.07 to 3.27)
Pettersson right elbow	3.9	3.8	3.7	4.8	.92 (-4.27 to 3.87)
Pettersson left elbow	2.6	4.1	5.2	5.0	.22 (-1.68 to 6.88)
Pettersson right knee	1.2	2.4	2.9	4.7	.33 (-1.93 to 5.33)
Pettersson left knee	2.5	2.8	2.4	4.4	.95 (-3.57 to 3.37)
Pettersson right ankle	6.1	5.1	3.5	4.7	.25 (-7.21 to 2.01)
Pettersson left ankle	5.9	5.6	5.2	5.9	.79 (-6.11 to 4.71)

[a]ABJR = annual bleeding joint rate; FIX = factor IX; FVIII = factor VIII; HCV = hepatitis type C virus; HIV = human immunodeficiency virus; HJHS = hemophilia joint health score; IU = international units; $t_{1/2}$ = half-life.

Table 3. Within-group Change From Baseline to Follow-Up.[a]

	Control		Intervention	
Descriptive Name	Mean (95% CI)	P^a	Mean (95% CI)	P^a
Joint Health (Hemophilia Joint Health Score)				
Right elbow	0.19 (-1.82 to 2.2)	.843	-1.79 (-3.8 to 0.22)	.078
Left elbow	0.27 (-0.53 to 1.06)	.490	-0.47 (-1.26 to 0.33)	.232
Right knee	-0.23 (-0.77 to 0.31)	.385	-0.27 (-0.81 to 0.27)	.308
Left knee	0.67 (0.09 to 1.26)	**.026**	-0.27 (-0.86 to 0.31)	.336
Right ankle	0.03 (-1.1 to 1.16)	.953	-0.33 (-1.46 to 0.8)	.543
Left ankle	-0.3 (-1.03 to 0.43)	.400	0.4 (-0.33 to 1.13)	.266
Total Score	0.99 (-1.97 to 3.95)	.490	-2.89 (-5.85 to 0.07)	.055
Isometric muscle strength (Kg)				
Elbow flexion left	-0.61 (-2.76 to 1.54)	.558	2.21 (0.06 to 4.36)	**.045**
Elbow flexion right	-1.1 (-3.35 to 1.15)	.317	2.86 (0.61 to 5.1)	**.016**
Elbow extension left	-0.61 (-1.8 to 0.59)	.299	1.6 (0.41 to 2.79)	**.011**
Elbow extension right	-0.77 (-1.7 to 0.17)	.102	1.95 (1.01 to 2.89)	**.000**
Knee extension left	-5.62 (-11.85 to 0.6)	.074	10.74 (4.52 to 16.97)	**.002**
Knee extension right	-5.08 (-10.51 to 0.36)	.065	12.72 (7.61 to 17.83)	**<.0001**
Knee flexion left	-0.92 (-3.14 to 1.29)	.392	5.77 (3.55 to 7.98)	**<.0001**
Knee flexion right	-2.05 (-8.13 to 4.04)	.487	1.65 (-4.09 to 7.4)	.550
Ankle plantarflexion left	-8.03 (-20.35 to 4.29)	.187	6.92 (-5.4 to 19.23)	.253
Ankle plantarflexion right	-11.19 (-21.48 to -0.9)	**.035**	3.21 (-7.08 to 13.5)	.519
Ankle dorsiflexion left	1.64 (-1.63 to 4.9)	.305	5.34 (2.07 to 8.61)	**.003**
Ankle dorsiflexion right	2.73 (-0.56 to 6.02)	.098	5.47 (2.17 to 8.76)	**.003**
Functional capacity (s)				
Timed Up and Go	-0.05 (-0.37 to 0.27)	.750	-0.68 (-1 to -0.36)	**.000**
Sit-to-stand	-0.25 (-0.67 to 0.18)	.238	-1.16 (-1.59 to -0.73)	**<.0001**
Range Of Motion (°)				
Knee extension left	-3.82 (-8.91 to 1.28)	.132	0.32 (-4.78 to 5.41)	.897
Knee extension right	-0.67 (-1.99 to 0.64)	.295	0.47 (-0.84 to 1.79)	.458
Knee flexion left	-1.39 (-4.56 to 1.77)	.366	3.06 (-0.1 to 6.22)	.057
Knee flexion right	-0.14 (-2.01 to 1.73)	.876	3.04 (1.17 to 4.91)	**.003**
Elbow flexion left	-1.34 (-5.11 to 2.43)	.464	1.37 (-2.4 to 5.14)	.453
Elbow flexion right	0.97 (-1.61 to 3.55)	.440	4.33 (1.75 to 6.91)	**.003**
Elbow extension left	1.49 (-3.91 to 6.89)	.569	3.61 (-1.79 to 9.01)	.176
Elbow extension right	-2.41 (-5.41 to 0.58)	.107	-1.22 (-4.22 to 1.77)	.402
Ankle plantarflexion left	2.53 (-1.04 to 6.11)	.153	1.93 (-1.64 to 5.51)	.269
Ankle plantarflexion right	-0.78 (-6.54 to 4.98)	.779	0.58 (-5.18 to 6.34)	.834
Ankle dorsiflexion left	1.23 (-1.54 to 4)	.362	-1.63 (-4.4 to 1.14)	.231
Ankle dorsiflexion right	1.69 (-4.75 to 8.13)	.587	6.61 (0.17 to 13.05)	**.045**
Kinesiophobia (Tampa Scale for kinesiophobia)				
Total score	-0.4 (-4.07 to 3.28)	.823	-1.23 (-5.11 to 2.65)	.512

[a]Bold letters denote statistically significant differences.

Table 4. Between-group Difference in the Change From Baseline to Follow-Up.

Descriptive Name	Control Mean Change Minus Intervention Mean Change (95% CI)	*P*[a]	Effect Size	Minimal Clinically Important Differences
Joint Health (Hemophilia Joint Health Score)				
Right elbow	1.98 (-0.87 to 4.84)	.161	0.4	1.0
Left elbow	0.73 (-0.43 to 1.9)	.203	0.2	0.8
Right knee	0.04 (-0.73 to 0.81)	.912	0.0	1.0
Left knee	0.95 (0.12 to 1.77)	**.027**	0.2	1.0
Right ankle	0.36 (-1.24 to 1.97)	.638	0.1	0.7
Left ankle	-0.7 (-1.73 to 0.34)	.173	0.2	0.7
Total Score	3.88 (-0.34 to 8.1)	.069	0.2	3.3
Isometric muscle strength (Kg)				
Elbow flexion left	-2.82 (-6.14 to 0.5)	.091	0.5	1.2
Elbow flexion right	-3.95 (-7.18 to -0.73)	**.019**	0.7	1.2
Elbow extension left	-2.21 (-3.93 to -0.49)	**.015**	0.4	1.1
Elbow extension right	-2.72 (-4.05 to -1.38)	**.001**	0.8	0.7
Knee extension left	-16.36 (-25.52 to -7.21)	**.002**	0.8	4.1
Knee extension right	-17.8 (-25.93 to -9.67)	**<.0001**	1.2	2.9
Knee flexion left	-6.69 (-9.86 to -3.52)	**<.0001**	1.1	1.2
Knee flexion right	-3.7 (-12.49 to 5.09)	.385	0.4	2.0
Ankle plantarflexion left	-14.95 (-32.51 to 2.61)	.090	0.5	5.8
Ankle plantarflexion right	-14.4 (-28.96 to 0.16)	.052	0.4	6.5
Ankle dorsiflexion left	-3.7 (-8.44 to 1.04)	.118	0.8	0.9
Ankle dorsiflexion right	-2.73 (-7.4 to 1.93)	.233	0.5	1.1
Functional capacity (s)				
Timed Up and Go	0.63 (0.18 to 1.09)	**.009**	0.5	0.3
Sit-to-stand	0.91 (0.31 to 1.52)	**.006**	0.5	0.4
Range Of Motion (°)				
Knee extension left	-4.14 (-11.48 to 3.2)	.251	0.7	1.1
Knee extension right	-1.15 (-3.01 to 0.72)	.212	0.1	2.6
Knee flexion left	-4.45 (-9.11 to 0.2)	.059	0.4	2.1
Knee flexion right	-3.18 (-5.82 to -0.54)	**.021**	0.1	7.1
Elbow flexion left	-2.71 (-8.14 to 2.72)	.307	0.2	2.4
Elbow flexion right	-3.37 (-7.03 to 0.3)	.070	0.4	1.9
Elbow extension left	-2.13 (-9.8 to 5.54)	.566	0.1	4.3
Elbow extension right	-1.19 (-5.43 to 3.04)	.561	0.1	4.2
Ankle plantarflexion left	0.6 (-4.46 to 5.65)	.806	0.0	2.9
Ankle plantarflexion right	-1.36 (-9.55 to 6.83)	.731	0.1	2.4
Ankle dorsiflexion left	2.86 (-1.13 to 6.85)	.149	0.4	1.3
Ankle dorsiflexion right	-4.92 (-14.06 to 4.22)	.272	0.6	1.7
Kinesiophobia (Tampa Scale for kinesiophobia)				
Total score	0.83 (-4.51 to 6.18)	.746	0.1	1.6

[a]Bold type denotes statistically significant differences.

Table 5. Perceived Changes After the Study (% Subjects).

	Control	Intervention
Overall pain status		
Very much improved	20	30
Much improved	0	40
Minimally improved	40	30
No change	40	0
Minimally worse	0	0
Much worse	0	0
Very much worse	0	0
Overall health status after the study		
Improved	10	100
No change	90	0
Worsened	0	0
Desire of practicing exercise		
Improved	10	100
No change	90	0
Worsened	0	0

FIGURE CAPTIONS

Figure. Intervention training exercises

1) Knee extension
2) Knee flexion
3) Ankle plantarflexion
4) Ankle dorsal flexion
5) Elbow flexion
6) Elbow extension
7) Shoulder abduction
8) Hip abduction