Original Research

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 the 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) 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 and increased progressively toward 15, 12, and finally 10 repetition maximum. The primary outcome was muscle strength. Secondary outcomes were the Timed "Up and Go" Test score, sit-to-stand, range of motion, Haemophilia Joint Health Score, 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 Timed "Up and Go" and sit-to-stand scores than the control group (moderate effect size), greater range of motion at the knee flexion with the right leg (trivial effect size), and better Haemophilia Joint Health Score 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 the intra-articular level,[2] initiating a vicious cycle of pain,[3] physical inactivity, muscle weakness, muscle atrophy, and increased bleeding risk.[4] Consequently, 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 with clotting 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 remain 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 1-repetition maximum) can improve muscular endurance or even maximal strength gains in untrained individuals, higher intensities (eg, 80% of 1-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 the 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 with clotting 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 shown 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, to our knowledge, 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 the 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.

Methods

Participants

The present study was a randomized controlled trial with 2 parallel groups. Participants between 18 and 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) individuals with severe hemophilia receiving prophylactic treatment; (3) willingness to exercise twice a week during the training program and to complete the pre- and post-program evaluations; (4) approval by their hematologist to participate in the exercise program; and (5) 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 programmed 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 $\geq$0.4 Bethesda unit); (8) another hemostatic defect; (9) need for major surgery; or (10) 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 Consolidated Standards of Reporting Trials (CONSORT) Statement.

Randomization and Allocation

After receiving a list with possible individuals from a medical doctor (neither involved in the testing nor training

Figure.
Intervention training exercises:
1) Knee extension
2) Knee flexion
3) Ankle plantar flexion
4) Ankle dorsiflexion
5) Elbow flexion
6) Elbow extension
7) Shoulder abduction
8) Hip abduction

sessions), the main researcher involved in the recruitment process approached the participants, explained the study to them, and asked if they would be willing to participate. Those agreeing (20 participants) 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) group. 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.

Intervention

The intervention consisted of a group-based training program for 2 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 72 hours. The participants with severe disease had their prophylactic treatment 1 to 26 hours before each training session. Sessions took place under the supervision of 2 physical therapists and a sport scientist and strength and conditioning specialist.

Control Group

The control group performed their usual daily activities for 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.

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 to 13 per joint, 0 being the normality and 13 the maximum joint alteration.[18] Pharmacokinetics were determined using Bayesian post hoc estimation of individualized pharmacokinetics values (half-life, peak level, and level at training session) obtained using the Web Accessible Population Pharmacokinetic Service for Hemophilia.[19]

Table 1.
Intervention Training Program[a]

Frequency	2 d/wk for 8 Weeks
Exercises	Knee extension, knee flexion, ankle plantar flexion, ankle dorsiflexion, elbow flexion, elbow extension, shoulder abduction, and hip abduction, all performed with full ROM and elastic bands (TheraBand CLX, The Hygienic Corporation, Akron, OH, USA)
Exercise order	In each session, exercises were performed in a different order and in a rotation, switching from 1 exercise to the next so that 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; number of reps decreased as intensity increased
Rest	1 min between sets and exercises
Intensity	Intensity progressively increased to gradually augment stimulation during intervention, starting with moderate intensity of 20 RM and increasing each 2 wk towards high intensities of 15RM, 12RM, and finally 10RM. Participants were asked to complete targeted no. of repetitions (eg, 20) with an elastic tension that would allow performing an additional repetition (eg, 21) once they stopped the exercise, ie, finishing the set staying 1 repetition below muscle failure. To achieve adequate exercise intensity during each exercise, elastic bands were prestretched to approx. 50% of initial length (initial length, 1.9 m) then different bands were added when needed to reach the desirable intensity. Red, blue, black, silver, and gold elastic band colors were allowed alone or in combination
Velocity	Moderate lifting velocity (approximately 1 s concentric and 1 s eccentric)

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

Participants were scheduled for 2 testing days: baseline and after 8 weeks. All measurements were performed at the university by the same 2 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, UK) and weight (Tanita model BF- 350, Tanita, 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 plantar flexion and dorsiflexion, and isometric elbow flexion and extension were assessed with a portable hand-held dynamometer (Nicholas Manual Muscle Tester, Lafayette Instruments, Lafayette, IN, USA) with tests performed against fixed resistance. These joints were selected since they are the most affected in people with hemophilia.[1] Specifically, for the knee extension and flexion, participants were seated with back support, with a 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 to excellent intra-rater reliability for knee flexors, with an intraclass correlation coefficient (ICC) range of 0.76 to 0.94 and excellent (ICC range of 0.92–0.97) for knee extensors.[20] For ankle dorsiflexion and plantar flexion, participants 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 plantar flexion, 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, participants 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 to excellent reliability, with ICCs of 0.87 and 0.88 to 0.92, respectively.[22]

Passive range of motion (ROM) was measured at the aforementioned joints, with a universal goniometer (Absolute Axis goniometer, Baseline Evaluation Instruments, White Plains, NY, USA) in accordance with the Haemophlia Joint Health Score 2.1 (HJHS 2.1) recommendations. The HJHS and the Tampa Scale for Kinesiophobia 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 α of .80 for the Tampa Scale for kinesiophobia total score.[24]

The Timed Up and Go (TUG) and the sit-to-stand tests 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 3 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 such as 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 3-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]

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 participants were required to detect at least a medium effect size (f = 0.35; d = 0.7).

Statistical Analyses

Descriptive data of participants 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. Participant was entered as random effect and fixed effects were group and 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 $< .05$ were accepted as statistically significant.

Effect size (Cohen d) was calculated and described as: <0.2 = trivial effect, 0.2 = small, 0.5 = moderate, and 0.8 = large. Minimal clinically important differences were calculated according to previous recommendations[36] by multiplying pooled baseline SD scores by 0.2.

Role of the Funding Source

The funders played no role in the design, conduct, or reporting of the study.

Results

Supplementary Figure 1 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 participant who had severe disease with daily prophylactic factor had a coverage level at training time of 37.8 IU/dL. The participant with mild disease had a coverage level at training time of 11.0 IU/dL (basal level). The other participants in 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 participants 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 2.
Descriptive Data of Participants at Baseline[a]

	Control (n = 10)		Intervention (n = 10)		*P* (95% CI)
	Mean	SD	Mean	SD	
Demographics and pharmacokinetics					
Age (y)	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]Bold type denotes statistically significant differences. 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]

Descriptive Name	Control		Intervention	
	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 plantar flexion left	−8.03 (−20.35 to 4.29)	.187	6.92 (−5.4 to 19.23)	.253
Ankle plantar flexion 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 plantar flexion left	2.53 (−1.04 to 6.11)	.153	1.93 (−1.64 to 5.51)	.269
Ankle plantar flexion 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 type denotes statistically significant differences.

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

Descriptive Name	Control Mean Change Minus Intervention Mean Change (95% CI)	P[a]	Effect Size	Minimal Clinically
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 plantar flexion left	−14.95 (−32.51 to 2.61)	.090	0.5	5.8
Ankle plantar flexion 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 plantar flexion left	0.6 (−4.46 to 5.65)	.806	0.0	2.9
Ankle plantar flexion 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 (% Participants)

	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

Table 5 shows complete perceived changes data. The intervention group showed a significantly greater overall pain reduction ($P = .037$), self-rated overall status ($P < .001$), and desire to exercise ($P < .001$) than the control group.

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 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 participants.[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 plantar-flexion 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 participants. Interestingly, dorsiflexion strength was the least affected strength test after our intervention. We only found 2 cases where muscle strength was increased in only 1 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 participants,[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, to our knowledge, no previous studies exist that aim to explain 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 to 7 days per 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 a control group[35] or the use of participants without hemophilia as controls[46] are clear limitations. Interestingly, 2 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 participants 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 in the TUG, sit-to-stand, or gait speed tests, whereas 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. By adding specific flexibility exercises, we could have expected to find greater ROM gains; however, our findings show some improvement after performing strength training only. 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 participants as Pettersson 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 of 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 participants 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 than the control group after finishing the study. 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 randomized controlled trials showed no clear pain reduction after an educational physical therapy 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 latter 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 exploring this outcome in people with hemophilia, to our knowledge, 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 other peers are key elements for participating 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 the plasma factor level should be between 15% and 30% when intensive sport activity is carried out.[58] However, most of the participants with severe disease 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 <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 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, as it depends 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 with clotting 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 these 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 lead 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 participants with chronic pain.[64] Unfortunately, no other intervention studies have evaluated kinesiophobia changes in people with hemophilia.

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 testing 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 participants and researchers to understand what was done and what caused the specific results.

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

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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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