Received: 29 September 2022 | Revised: 10 November 2022 | Accepted: 14 November 2022

DOI: 10.1111/ejh.13900

ORIGINAL ARTICLE

European Journal of Haematology

WILEY

Effectiveness of progressive moderate-vigorous intensity elastic resistance training on quality of life and perceived functional abilities in people with hemophilia: Secondary analysis of a randomized controlled trial

Carlos Cruz-Montecinos[1,2] | Sofía Pérez-Alenda[1,3] | José Casaña[4] | Juan J. Carrasco[1,5] | Lars L. Andersen[6,7] | Rubén López-Bueno[6,8] | Rodrigo Nuñez-Cortés[1,9,10] | Santiago Bonanad[3] | Felipe Querol[1,3] | Joaquín Calatayud[4,6]

[1]Physiotherapy in Motion, Multispeciality Research Group (PTinMOTION), Department of Physiotherapy, University of Valencia, Valencia, Spain

[2]Laboratory of Clinical Biomechanics, Department of Physical Therapy, Faculty of Medicine, University of Chile, Santiago, Chile

[3]Haemostasis and Thrombosis Unit, Universitary and Polytechnic Hospital La Fe, Valencia, Spain

[4]Exercise Intervention for Health Research Group (EXINH-RG), Department of Physiotherapy, University of Valencia, Valencia, Spain

[5]Intelligent Data Analysis Laboratory, University of Valencia, Valencia, Spain

[6]National Research Centre for the Working Environment, Copenhagen, Denmark

[7]Sport Sciences, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

[8]Department of Physical Medicine and Nursing, University of Zaragoza, Zaragoza, Spain

[9]Department of Physical Therapy, Faculty of Medicine, University of Chile, Santiago, Chile

[10]Service of Physical Therapy, Hospital Clínico Florida, Santiago, Chile

Correspondence
Sofía Pérez-Alenda, Department of Physiotherapy, Universitat de València, C/Gascó Oliag 5, CP: 46010 Valencia, Spain.
Email: sofia.perez-alenda@uv.es

Funding information
Baxalta US Inc, Banockburn, Illinois, (USA)

Abstract

Introduction and Aim: Strength exercise training is advised for people with hemophilia (PWH); however, few studies have been published and have methodological limitations. The purpose of this study was to evaluate the effectiveness of progressive elastic resistance training on quality of life and perceived functional abilities in PWH.

Methods: Participants were randomly allocated to the intervention ($n = 10$) or control ($n = 10$) group. The intervention group performed progressive moderate-vigorous elastic resistance training (2 days/week, a total of 8 weeks), focusing on the muscles of the knee, elbow, and ankle joints. The control group continued its usual daily activities for 8 weeks. Quality of life (A36 Hemofilia-QoL®) and perceived functional abilities (Haemophilia Activities List) were assessed at baseline and an 8-week follow-up.

Results: The intervention group improved the quality-of-life dimension of joint damage perception in comparison to the control group ($p = .015$, large effect size). Regarding perceived functional abilities, the intervention group improved lying,

sitting, kneeling, and standing ($p = .006$, small effect size), and complex lower extremities activities (i.e., walking short and long-distance, and up-down stairs) ($p = .006$, small effect size) compared to the control group. No other significant differences were observed.

Conclusions: Eight weeks of progressive moderate-vigorous elastic resistance training in PWH improve the quality-of-life dimension of joint damage perception and perceived functional abilities (lying/sitting/kneeling/standing, and complex lower extremities activities). Our results suggest a limited effect of the program on the other items of quality of life measured by the questionnaire as emotional functioning, mental health, and social relationships. Importantly, no serious adverse effects occurred.

KEYWORDS

Arthropathy, exercise, hemophilia, health-related quality of life, patient outcome measure, rehabilitation, resistance training

1 | INTRODUCTION

Hemophilia is a genetic bleeding disorder related to a deficit of factor VIII (hemophilia A) or factor IX (hemophilia B). This disease causes spontaneous bleeding episodes, especially on the intra-articular level. The repetitive intra-articular bleeding generates deterioration in bones, synovial membrane, and cartilage tissue, resulting in a hemophilic arthropathy.[1] Hemophilic arthropathy is characterized by changes in the musculoskeletal system, producing a vicious cycle of pain, physical inactivity, muscle weakness, muscle atrophy, and increased risk of bleeding.[2,3] These changes often have deleterious consequences for the quality of life and functional abilities.[4–7]

At the current stage of research, exercise (e.g., strength training) is recommended as a preventive and rehabilitative treatment in people with hemophilia (PWH).[4–6,8] Importantly, strength training can be performed to promote these changes without bleedings or adverse events.[6,9,10] Furthermore, this type of training may increase muscle mass, joint range of motion, and lower limb proprioception, as well as reduce pain and bleeds, improving physical function.[6,8] However, previous literature evaluating the effect of exercise training in PWH on quality-of-life or daily life functional abilities in PWH is scarce.[11,12] For instance, Cuesta-Barriuso and coworkers reported that educational intervention with home-based exercises, including low-intensity exercises and strength training, improved the domain's physical health and treatment satisfaction based on quality-of-life questionnaires.[12] In addition, the authors found improved joint damage and treatment difficulties within a quality-of-life questionnaire. However, the aforementioned study conducted a combined intervention with several components, which warrants new studies focused on solely exercise. Particularly, evidence on the effects of moderate-vigorous training intensities on quality of life in PWH remains unknown.

Recent research has suggested elastic resistance to be an excellent alternative to conventional strength training for PWH.[9,13] Compared to conventional exercise machines, elastic resistance is safer, cheaper, and more feasible in different environments. Laboratory studies using electromyography further show similar levels of muscle activity when using elastic bands compared with conventional weight training.[14,15] However, few studies included elastic resistance training in PWH. A recent study reported that a multimodal intervention with psychological sessions in combination with home exercises including elastic resistance training improved the quality of life in PWH.[16] However, the effects of elastic resistance training solely to improve the quality of life, and functional abilities in PWH have not previously been investigated.

The aim of this study was to evaluate the effectiveness of progressive moderate-vigorous elastic resistance training on quality of life and perceived functional abilities in PWH. We hypothesized that the program would be effective in increasing the quality of life and perceived functional abilities in PWH.

2 | METHODS

2.1 | Study design

A randomized controlled trial with two parallel groups was conducted. Participants were randomly allocated following simple randomization procedures (computerized random numbers) with an allocation ratio of 1:1 to either intervention (progressive elastic resistance training) or control (usual daily activities).

Participants were recruited from Hemostasis and Thrombosis Unit of the University and Polytechnic Hospital The study was registered in ClinicalTrials.gov (NCT02781233) and adheres to the Consolidated Standards of Reporting Trials (CONSORT) Statement. Different data from the same project has been previously published in another article, which addressed a different research question.[10] The current study was conducted from October 2017 to June 2018.

2.2 | Participants

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 latest amendment in 2008.

Key inclusion criteria were (1) diagnosis of mild, moderate, or severe hemophilia A or B between 18 and 60 years old; (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 eight 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; (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; or (10) withdrawal of informed consent.

2.3 | Primary outcome measures

The quality of life and perceived functional abilities were subjectively assessed at baseline and at the 8-week follow-up by the same physical therapist, who was blinded to group allocation and was not involved in the training supervision to avoid any possible risk of bias.

Quality of life was subjectively assessed with the specific self-reported questionnaire A36 Hemofilia-QoL®. This questionnaire has 36 questions with response options of a five-point Likert scale and offers a global score and different scores in nine dimensions of health-related quality of life: physical health, daily activities, joint damage, pain, treatment satisfaction, treatment difficulties, emotional functioning, mental health and relationships, and social activity. Higher scores denote a better quality of life in patients. Psychometric characteristics of the A36 Hemofilia-QoL® showed good values in terms of reliability, internal consistency ($\alpha = .95$), test–retest reliability ($r = .92$; $p = .001$), and validity.[17] It has excellent concurrent validity (with the SF-36 Health Survey), external criteria validity (clinical status), and sensitivity to change (change in health status).[17]

Functional abilities were subjectively assessed with the Haemophilia Activities List (HAL). The list contains a hemophilia-specific self-assessment questionnaire providing the patient's self-perceived functional ability.[18] It contains 42 multiple-choice questions in seven domains: (1) lying/sitting/kneeling/standing; (2) functions of the legs; (3) functions of the arms; (4) use of transportation; (5) self-care; (6) household tasks; and (7) leisure activities and sports. In addition to the domain scores, four summary scores are generated for upper extremities, lower extremities, complex lower extremity functionality, and sum of points. Higher scores denote better functionality. The HAL demonstrated good values for internal consistency on seven HAL domains ($\alpha = .61–0.96$), and convergent validity ($r = .47–.84$) when compared to questionnaires to assess a patient's self-perceived functional ability (Dutch-Arthritis Impact Measurement Scales and the Impact on Participation and Autonomy questionnaire). On the contrary, construct validity shows lower values when compared to performance tests (button test, 50-m walking test, timed-up-and-go test, and figure-eight walking test) ($r = .23–.77$).[18]

2.4 | Secondary outcome measures

The following variables were collected: age, height, body mass index, type and severity of hemophilia, pharmacological treatment (prophylaxis or demand and factor dose IU/Kg), comorbidities (human immunodeficiency virus and hepatitis type C virus infection), knee and ankle replacement, and joint health by Hemophilia Joint Health Score (HJHS) and Pettersson score.[19,20] HJHS is a clinical scale that scores each joint from 0 to 20 points, with higher scores reflecting worse conditions (maximum score of 120 points, sum of elbows, knees, and ankles). Pettersson score evaluates radiologically different elements of the articular alteration by using an additive score of 0 to 13 per joint, with 0 indicating normality and 13 indicating maximum joint alteration (upper limb; elbows and lower limbs; knees and ankles).[20,21]

3 | TREATMENTS

The complete details of the progressive elastic resistance program are reported elsewhere.[10] Briefly, the intervention group consisted of a supervised group-based training program for 2 days per week for a total of 8 weeks, with three sets of each of the eight exercises, especially focused on increasing muscle strength in the knee, elbow, and ankle joints.[10] Intensity progressively increased every 2 weeks from 20 to 15, 12, and finally 10 repetitions (staying always one repetition below muscle failure). Exercises were performed with full available ROM, with 1-min rest between them, and at 1-s concentric/1-s eccentric contraction velocity. Sessions were performed at the same time of the day at the university and were separated by 72 h. Sessions took place under de supervision of two physical therapists and a certified strength and conditioning specialist.

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.[10]

4 | 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 previous

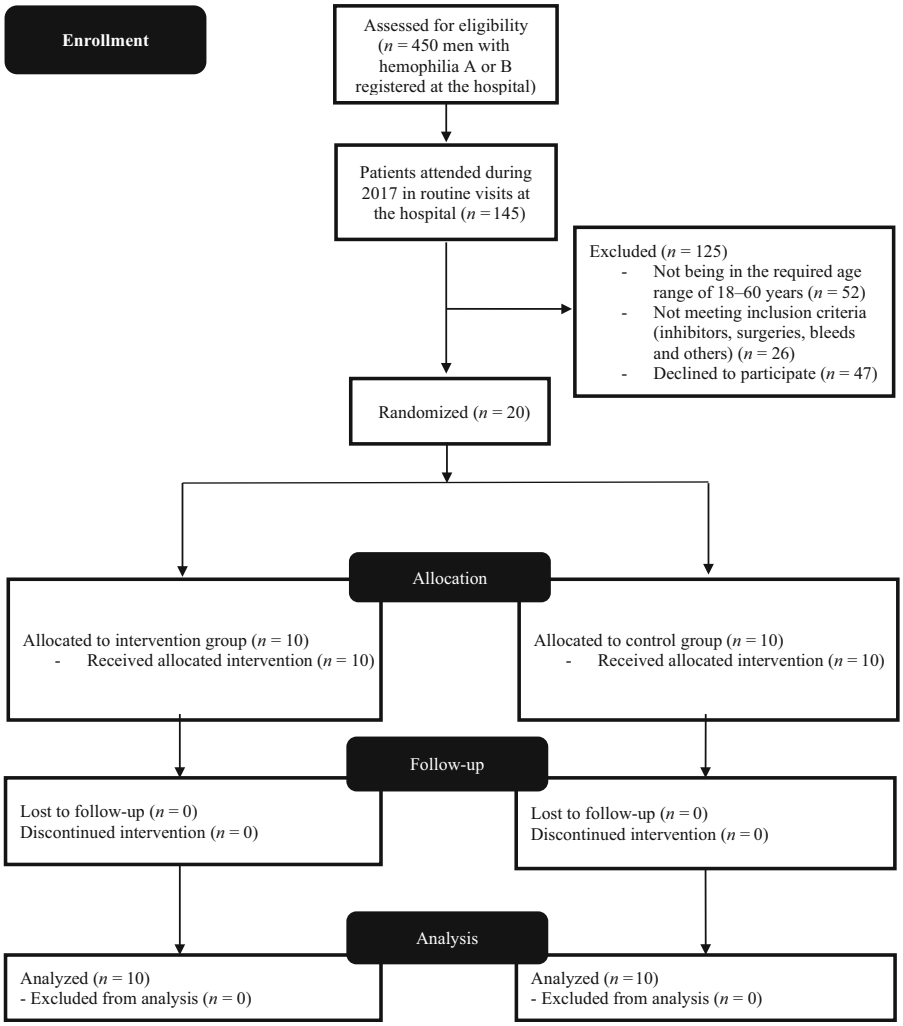

FIGURE 1 Flow diagram of the progress through the phases of the study

research as a reference. In the study of Mulvany et al.,[22] 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 ($\alpha = .05$) and 20% beta risk ($\beta = .2$; power = 0.80), a total of 20 subjects were required to detect at least a medium effect size ($f = 0.35$; $d = 0.7$).

4.1 | Statistical analyses

Descriptive data of subjects at baseline were compared using unpaired t-tests. The change score from baseline to follow-up between intervention and control was evaluated using linear mixed models (Proc Mixed, SAS version 9.4) according to the intention-to-treat principle. Subjects were entered as random effects. Fixed effects were (1) the group and (2) the baseline value of the outcome variable. The estimation method restricted maximum likelihood with degrees of freedom based on the Satterthwaite 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 the variance component. *p*-values less than .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 by multiplying pooled baseline standard deviation scores by 0.2.[23]

5 | RESULTS

Figure 1 shows the complete flow chart diagram of the study progress. Table 1 shows complete demographic and descriptive data. No significant between-group differences were found between these variables. Participants had no previous experience with elastic resistance training. No serious adverse effects occurred. All the participants in the intervention group complied with all the training sessions.

Using the specific questionnaire A36 Hemofilia-QoL®, we found that the intervention group improved the joint damage dimension in comparison to the control group (Table 2). The overall quality of life

TABLE 1 Descriptive data of subjects at baseline

	Control ($n = 10$)		Intervention ($n = 10$)		p-value (95% CI)
	Mean	SD	Mean	SD	
Demographics and pharmacokinetics					
Age (years)	39.1	8.4	36.3	10.5	.52 (−11.76 to .16)
Height (cm)	174.3	7.6	172.8	7.9	.67 (−8.80 to 5.80)
Body mass index (kg/m^2)	27.0	7.0	27.2	6.3	.95 (−6.46 to .06)
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	-	-	-
HIV (n)	4		4		-
HCV (n)	5		6		-
Musculoskeletal data					
Total knee replacement (n)	0		1		-
Total ankle replacement (n)	1		0		-
ABJR	1.2	1.2	0.7	0.8	.30 (−1.48 to .48)
HJHS elbows	5.5	5.6	3.3	3.4	.08 (−0.82 to 5.12)
HJHS knees	3.5	5.6	2.6	4.2	.28 (−2.26 to 4.06)
HJHS ankles	5.2	3.3	5.6	3.6	.34 (−2.64 to 1.74)
Total HJHS	23.0	10.5	28.2	19.3	.47 (−20.08 to 9.68)
Pettersson upper limbs	3.3	3.6	4.5	4.6	.52 (−5.07 to 2.67)
Pettersson lower limbs	3.9	2.5	3.5	3.5	.76 (−2.40 to 3.25)
Quality of life					
Physical health	20.7	6.8	25.2	3.6	
Daily activities	8.6	4.6	11.0	4.3	
Joints	6.1	2.6	8.3	1.7	
Pain	3.6	2.9	4.5	2.2	
Satisfaction with treatment	6.5	1.2	6.9	1.3	
Difficulties with treatment	11.5	2.1	12.0	2.4	
Emotional functioning	13.3	5.2	9.9	6.7	
Mental health	8.9	3.5	7.6	4.0	
Social relationships	16.3	3.1	14.6	6.0	
Overall quality of life	95.5	25.8	100.0	21.0	
Functional abilities (Haemophilia Activities List)					
Lying/sitting/kneeling/standing	80.5	18.7	70.0	27.2	
Functions of the legs	71.6	23.5	70.4	24.4	
Functions of the arms	88.5	19.6	79.0	24.2	
Use of transportation	92.7	13.9	73.3	24.7	
Self-care	97.2	4.6	84.8	23.4	
Household tasks	94.7	18.5	78.0	19.5	
Leisure activities and sports	80.3	18.5	78.0	19.5	
Upper extremity activities	93.3	10.2	82.2	23.2	
Basic lower extremity activities	79.0	24.9	81.8	22.3	
Complex lower extremity activities	67.1	25.9	55.8	33.0	
Sum score	84.2	11.6	76.2	20.0	

Abbreviations: 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 unit; $t_{1/2}$, half-life.

TABLE 2 Results of *quality of life and functional abilities* analysis

	Within-group change from baseline to follow-up—control		Within-group change from baseline to follow-up—intervention		Between-group difference in the change from baseline to follow-up—control-intervention			
Descriptive name	**Mean (95% CI)**	***p*-value**	**Mean (95% CI)**	***p*-value**	**Mean (95% CI)**	***p*-value**	**Effect size**	**Minimal clinically important differences**
Quality of life (*A36 Hemofilia-QoL*)								
Physical health	0.4 (−1.86 to 2.66)	.712	2.4 (0.14 to 4.66)	**.039**	−2 (−5.32 to 1.33)	.223	0.4	1.1
Daily activities	0.52 (−1.88 to 2.92)	.654	2.08 (−0.32 to 4.48)	.086	−1.56 (−5.03 to 1.91)	.355	0.4	0.9
Joints	−0.11 (−1.33 to 1.1)	.845	2.21 (1 to 3.43)	**.001**	−2.33 (−4.15 to −0.51)	**.015**	1.0	0.4
Pain	0.13 (−0.57 to 0.84)	.700	0.97 (0.26 to 1.67)	**.010**	−0.84 (−1.84 to 0.17)	.097	0.3	0.5
Satisfaction with treatment	−0.19 (−0.75 to 0.37)	.480	0.29 (−0.27 to 0.85)	.286	−0.48 (−1.27 to 0.31)	.217	0.4	0.2
Difficulties with treatment	0.2 (−1.21 to 1.6)	.769	1.1 (−0.3 to 2.51)	.117	−0.9 (−2.9 to 1.09)	.353	0.4	0.5
Emotional functioning	0.97 (−1.64 to 3.58)	.443	3.33 (0.72 to 5.94)	**.015**	−2.36 (−6.12 to 1.41)	.204	0.4	1.2
Mental health	−0.55 (−2.36 to 1.26)	.531	1.15 (−0.66 to 2.96)	.198	−1.7 (−4.28 to 0.88)	.183	0.5	0.8
Social relationships	0.4 (−0.69 to 1.49)	.449	0.6 (−0.49 to 1.69)	.264	−0.2 (−1.76 to 1.36)	.793	0.0	1.0
Overall quality of life	2.91 (−4.9 to 10.71)	.443	12.99 (5.19 to 20.8)	**.003**	−10.09 (−21.15 to 0.98)	.071	0.4	4.7
Functional abilities (*Haemophilia Activities List*)								
Lying/sitting/kneeling/standing	−3.55 (−8.17 to 1.07)	.123	6.3 (1.68 to 10.92)	**.010**	−9.85 (−16.47 to −3.23)	**.006**	0.4	4.7
Functions of the legs	−1.28 (−6.9 to 4.33)	.636	4.23 (−1.39 to 9.84)	.131	−5.51 (−13.45 to 2.43)	.161	0.2	4.8
Functions of the arms	0.54 (−6.8 to 7.88)	.878	5.46 (−1.88 to 12.8)	.135	−4.92 (−15.42 to 5.59)	.337	0.2	4.4
Use of transportation	2.47 (−5.24 to 10.19)	.508	2.86 (−4.85 to 10.57)	.445	−0.38 (−11.9 to 11.13)	.945	0.0	4.0
Self-care	−0.31 (−8.96 to 8.34)	.941	−0.09 (−8.74 to 8.56)	.983	−0.22 (−12.88 to 12.44)	.971	0.0	3.4
Household tasks	−0.39 (−7.06 to 6.28)	.903	1.52 (−5.15 to 8.19)	.636	−1.91 (−11.59 to 7.77)	.682	0.1	3.5
Leisure activities and sports	4.59 (0.73 to 8.45)	**.023**	9.81 (5.95 to 13.67)	**<.0001**	−5.22 (−10.69 to 0.24)	.060	0.3	3.8
Upper extremity activities	−0.19 (−7.65 to 7.27)	.958	2.63 (−4.82 to 10.09)	.466	−2.82 (−13.63 to 7.99)	.589	0.2	3.6
Basic lower extremity activities	−0.48 (−6.6 to 5.64)	.870	4.68 (−1.44 to 10.8)	.125	−5.16 (−13.83 to 3.5)	.226	0.2	4.7
Complex lower extremity activities	−2.65 (−6.73 to 1.44)	.190	6.03 (1.95 to 10.12)	**.006**	−8.68 (−14.52 to −2.84)	**.006**	0.3	5.9
Sum score	−0.56 (−5.17 to 4.05)	.800	5.07 (0.46 to 9.68)	**.033**	−5.64 (−12.26 to 0.98)	.090	0.3	3.3

Note: Bold letters denote statistically significant differences.

showed a borderline significant ($p = .071$) result favoring the intervention with a small effect size and a clinically important difference (Table 2).

Using the HAL - questionnaire, the perceived functional abilities (i.e., lying, sitting, kneeling, and standing) and complex lower extremities activities (i.e., walking short and long-distance, walking on soft and uneven surfaces, up-down stairs, running, and jumping) showed an increase in the intervention group compared to the control group (Table 2). Leisure activities and sports showed a tendency to increase after the intervention, with a borderline significant ($p = .060$) result favoring intervention with a small effect size and clinically important difference (Table 2). No other significant differences were observed in A36 Hemofilia-QoL and HAL questionnaires.

6 | DISCUSSION

The main findings of the present study are that progressive moderate-to-vigorous intensity elastic resistance training improves the quality-of-life dimension of joint damage perception, and functional abilities (lying/sitting/kneeling/standing, and complex lower extremities activities). The present results partly support our hypothesis that the program would be effective in increasing the quality of life and perceived functional abilities in PWH.

Regarding the effect on the quality of life, only joint damage perception improved in the intervention compared with the control group. In contrast, using the same questionnaire, a previous study in PWH reported improved perception of physical health, daily activities, joint damage perception, pain, emotional functioning, and overall quality of life after a 15-week home exercise program (once a day, 6 days a week) with low-intensity exercises with 20–25 repetitions and educational sessions every two weeks.[12] In addition, a recent study found improved quality of life from a combined program including psychological components (four sessions of 2 h) and three at-home sessions of 1 h of low-intensity exercise per week (10 supervised and 38 self-monitored) during 4 months.[16] It is plausible that the aforementioned studies had a more remarkable effect due to the longer intervention performed and the educational or psychological programs, in spite of the lower exercise intensity used. However, we want to highlight the relevance of finding changes after only 8 weeks with one type of intervention. In addition, the borderline significant result favoring the intervention on the overall quality of life score, with a small effect size and a clinically important difference can be relevant too. While our training program previously reported enhanced objectively measured physical function and overall pain,[10] which should translate into better physical function and quality of life, it is plausible that the sensitivity of the questionnaire to document these effects is not sufficient. In addition, the multiple dimensions might hide such specific improvements. Our findings are in line with a previous study using another quality-of-life questionnaire the Short Form Health Survey (SF-36) in PWH, where authors reported that the 12 weeks of Nordic Walking for 30 min three times a week did not increase this outcome.[24] The effectiveness of elastic resistance to improve the quality of life has been reported in different diseases such as chronic obstructive pulmonary disease,[25] or systemic lupus erythematosus.[26] However, in other diseases such as end-stage renal disease, some elastic resistance training programs did not increase the quality of life but improved physical functioning.[27] It should be considered that strengthening exercise may not be the only factor to improve quality of life. For instance, quality of life in PWH may not depend only on the increasing strength capacity, since pain, kinesiophobia, catastrophism, and hemophilia severity among other factors may have an important influence.[7]

In this study, using the HAL questionnaire, we observed that the intervention group improved their perceived functional abilities (i.e., lying, sitting, kneeling, standing), and complex lower extremities activities. Furthermore, we observed a borderline significant result favoring the intervention of leisure activities and sports with a small effect size and a clinically important difference. In contrast, we did not observe an increase in perceived functional abilities in the upper extremity. The effectiveness of elastic resistance training to promote strengthening comparing conventional resistance is well documented.[25,28] We have previously published (among the same participants) improvements after progressive moderate-to-vigorous intensity elastic resistance on muscle strength in elbows and knees and perceived changes in pain, overall status, and desire to exercise.[10] However, we previously found[10] that the greatest strength improvement was achieved in the knees, which might partly explain the present results. Furthermore, the limited improvement in perceived functional abilities in the upper extremity may be explained by other factors that may affect the functionality as the limited range of motion in the elbow in some patients.[29,30] Importantly, resistance training in PWH has been shown that not only improve joint function but may also have a protective effect[5,31] and enhance muscle coordination, which is affected in PWH,[32] helping to improve their functional and walking abilities.[33]

The main limitation of the present study is the low sample size. A greater sample size may have helped to generalize our results. It should be mentioned that nine within-group significant changes occurred in the intervention group, while this was only the case for one significant change in the control group. By contrast, only three between-group differences were significant. Thus, larger studies with more statistical power may be needed to document significant between-group changes in these variables. However, the sample size obtained was sufficient according to a priori power analysis and considering that hemophilia is a rare disease. Future studies with greater sample sizes are needed to corroborate the results of this study. In addition, it should be considered that the questionnaires used might be too general and subjective and thus limited to assess some changes induced by an exercise intervention. Importantly, to the authors' current knowledge, this study is the first to show the effectiveness of progressive moderate-to-vigorous intensity elastic resistance training on quality of life and perceived functional abilities in PWH.

7 | CONCLUSIONS

Eight weeks of progressive moderate-vigorous elastic resistance training in PWH improve the quality-of-life dimension of joint damage perception and perceived functional abilities (lying/sitting/kneeling/

standing, and complex lower extremities activities). Our results suggest a limited effect of the program on the other items of quality of life measured by the questionnaire as emotional functioning, mental health, and social relationships. Importantly, no serious adverse effects occurred. These results may help clinicians and researchers regarding the implementation of strength programs using elastic resistances in PWH. Future studies are needed to understand the effects of resistance training in PWH, alone or in combination with other modalities.

FUNDING INFORMATION

This study was supported by an investigator-initiated research grant (H15-29504) from Baxalta US Inc., Bannockburn, Illinois, USA, now part of the Takeda group of companies. The funders played no role in the design, conduct, or reporting of the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Sofía Pérez-Alenda https://orcid.org/0000-0002-0841-5767
Juan J. Carrasco https://orcid.org/0000-0002-0740-3772
Santiago Bonanad https://orcid.org/0000-0002-8390-8211

REFERENCES

1. van Vulpen LFD, Holstein K, Martinoli C. Joint disease in haemophilia: pathophysiology, pain and imaging. *Haemophilia*. 2018;24(suppl 6):44-49.
2. Roussel NA. Gaining insight into the complexity of pain in patients with haemophilia: state-of-the-art review on pain processing. *Haemophilia*. 2018;24(suppl 6):3-8.
3. Roosendaal G, Lafeber FP. Pathogenesis of haemophilic arthropathy. *Haemophilia*. 2006;12(suppl 3):117-121.
4. Forsyth AL, Quon DV, Konkle BA. Role of exercise and physical activity on haemophilic arthropathy, fall prevention and osteoporosis. *Haemophilia*. 2011;17:e870-e876.
5. Harris S, Boggio LN. Exercise may decrease further destruction in the adult haemophilic joint. *Haemophilia*. 2006;12:237-240.
6. Siqueira TC, Dominski FH, Andrade A. Effects of exercise in people with haemophilia: an umbrella review of systematic reviews and meta-analyses. *Haemophilia*. 2019;25:928-937.
7. Ucero-Lozano R, López-Pina JA, Ortiz-Pérez A, Cuesta-Barriuso R. Quality of life and its predictors among adult patients with haemophilic arthropathy. An observational study. *BMC Musculoskelet Disord*. 2021;22:448. doi:10.1186/s12891-021-04319-0
8. Wagner B, Krüger S, Hilberg T, et al. The effect of resistance exercise on strength and safety outcome for people with haemophilia: a systematic review. *Haemophilia*. 2020;26:200-215.
9. Calatayud J, Pérez-Alenda S, Carrasco JJ, et al. Feasibility, safety and muscle activity during flywheel vs traditional strength training in adult patients with severe haemophilia. *Haemophilia*. 2021;27:e102-e109.
10. Calatayud J, Pérez-Alenda S, Carrasco JJ, et al. Safety and effectiveness of progressive moderate-to-vigorous intensity elastic resistance training on physical function and pain in people with hemophilia. *Phys Ther*. 2020;100(9):1632-1644. doi:10.1093/ptj/pzaa106
11. Runkel B, Von Mackensen S, Hilberg T. RCT—subjective physical performance and quality of life after a 6-month programmed sports therapy (PST) in patients with haemophilia. *Haemophilia*. 2017;23:144-151. doi:10.1111/hae.13079
12. Cuesta-Barriuso R, Torres-Ortuño A, Nieto-Munuera J, López-Pina JA. Effectiveness of an educational physiotherapy and therapeutic exercise program in adult patients with hemophilia: a randomized controlled trial. *Arch Phys Med Rehabil*. 2017;98:841-848.
13. Calatayud J, Martín-Cuesta J, Carrasco JJ, et al. Safety, fear and neuromuscular responses after a resisted knee extension performed to failure in patients with severe haemophilia. *J Clin Med Res*. 2021;10(12):2587. doi:10.3390/jcm10122587
14. Lima FF, Camillo CA, Gobbo LA, et al. Resistance training using low cost elastic tubing is equally effective to conventional weight Machines in Middle-Aged to older healthy adults: a quasi-randomized controlled clinical trial. *J Sports Sci Med*. 2018;17:153-160.
15. Calatayud J, Pérez-Alenda S, Carrasco JJ, et al. Electromyographic and safety comparisons of common lower limb rehabilitation exercises for people with hemophilia. *Phys Ther*. 2020;100:116-126.
16. García-Dasí M, Pérez-Alenda S, Carrasco JJ, et al. Effects of a non-pharmacological approach for chronic pain management in patients with haemophilia: efficacy of cognitive-behavioural therapy associated with physiotherapy. *Haemophilia*. 2021;27:e357-e367.
17. Remor E, Arranz P, Quintana M, et al. Psychometric field study of the new haemophilia quality of life questionnaire for adults: the "Hemofilia-QoL". *Haemophilia*. 2005;11:603-610.
18. van Genderen FR, Westers P, Heijnen L, et al. Measuring patients' perceptions on their functional abilities: validation of the Haemophilia Activities List. *Haemophilia*. 2006;12:36-46.
19. Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. *Haemophilia*. 2006;12:518-525.
20. Manco-Johnson MJ, Pettersson H, Petrini P, et al. Physical therapy and imaging outcome measures in a haemophilia population treated with factor prophylaxis: current status and future directions. *Haemophilia*. 2004;10:88-93. doi:10.1111/j.1365-2516.2004.00978.x
21. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop Relat Res*. 1980;149:153-159.
22. Mulvany R, Zucker-Levin AR, Jeng M, et al. Effects of a 6-week, individualized, supervised exercise program for people with bleeding disorders and hemophilic arthritis. *Phys Ther*. 2010;90:509-526.
23. Page P. Beyond statistical significance: clinical interpretation of rehabilitation research literature. *Int J Sports Phys Ther*. 2014;9:726-736.
24. Salim M, Brodin E, Spaals-Abrahamsson Y, Berntorp E, Zetterberg E. The effect of Nordic Walking on joint status, quality of life, physical ability, exercise capacity and pain in adult persons with haemophilia. *Blood Coagul Fibrinolysis*. 2016;27:467-472.
25. de Lima FF, Cavalheri V, Silva BSA, et al. Elastic resistance training produces benefits similar to conventional resistance training in people with chronic obstructive pulmonary disease: systematic review and meta-analysis. *Phys Ther*. 2020;100:1891-1905.
26. Abrahão MI, Gomiero AB, Peccin MS, Grande AJ, Trevisani VFM. Cardiovascular training vs. resistance training for improving quality of life and physical function in patients with systemic lupus erythematosus: a randomized controlled trial. *Scand J Rheumatol*. 2016;45:197-201.
27. da Costa Rosa CS, Nishimoto DY, GDE S, Ramirez AP, Carletti CO, et al. Effect of continuous progressive resistance training during hemodialysis on body composition, physical function and quality of life in end-stage renal disease patients: a randomized controlled trial. *Clin Rehabil*. 2018;32:899-908. doi:10.1177/0269215518760696
28. Lopes JSS, Machado AF, Micheletti JK, de Almeida AC, Cavina AP, Pastre CM. Effects of training with elastic resistance versus conventional resistance on muscular strength: a systematic review and meta-analysis. *SAGE Open Med*. 2019;7:2050312119831116.

29. Tat AM, Can F, Tat NM, Sasmaz HI, Antmen AB. The effects of manual therapy and exercises on pain, muscle strength, joint health, functionality and quality of life in haemophilic arthropathy of the elbow joint: a randomized controlled pilot study. *Haemophilia*. 2021; 27:e376-e384.
30. Chen CM, Huang KC, Chen CC, et al. The impact of joint range of motion limitations on health-related quality of life in patients with haemophilia A: a prospective study. *Haemophilia*. 2015;21:e176-e184.
31. Schäfer GS, Valderramas S, Gomes AR, Budib MB, Wolff ÁLP, Ramos AAT. Physical exercise, pain and musculoskeletal function in patients with haemophilia: a systematic review. *Haemophilia*. 2016; 22:e119-e129.
32. Cruz-Montecinos C, Pérez-Alenda S, Cerda M, Maas H. Neuromuscular control during gait in people with haemophilic arthropathy. *Haemophilia*. 2019;25:e69-e77.
33. Hruda KV, Hicks AL, McCartney N. Training for muscle power in older adults: effects on functional abilities. *Can J Appl Physiol*. 2003;28:178-189.

How to cite this article: Cruz-Montecinos C, Pérez-Alenda S, Casaña J, et al. Effectiveness of progressive moderate-vigorous intensity elastic resistance training on quality of life and perceived functional abilities in people with hemophilia: Secondary analysis of a randomized controlled trial. *Eur J Haematol*. 2023;110(3):253-261. doi:10.1111/ejh.13900