Received: 28 April 2022 | Revised: 12 September 2022 | Accepted: 4 October 2022

DOI: 10.1111/hae.14683

Haemophilia WFH WILEY

ORIGINAL ARTICLE

Muskuloskeletal

180-degree immersive VR motion visualization in the treatment of haemophilic ankle arthropathy

Roberto Ucero-Lozano[1] | **Raúl Pérez-Llanes**[2] | **José Antonio López-Pina**[3] | **Rubén Cuesta-Barriuso**[4,5]

[1]Department of Physiotherapy, European University of Madrid, Madrid, Spain

[2]Department of Physiotherapy, Catholic University San Antonio-UCAM, Murcia, Spain

[3]Department of Basic Phycology and Methodology, University of Murcia, Murcia, Spain

[4]Department of Surgery and Medical-Surgical Specialties, University of Oviedo, Oviedo, Spain

[5]Department of Surgery and Medical-Surgical Specialties, Faculty of Medicine, University of Oviedo, Oviedo, Spain

Correspondence
Rubén Cuesta-Barriuso, Department of Surgery and Medical-Surgical Specialties, Faculty of Medicine, University of Oviedo, Campus de El Cristo s/n, Faculty of Medicine, 33006 Oviedo, Spain.
Email: cuestaruben@uniovi.es

Trial registration: ClinicalTrials.gov Protocol Registration, NCT04549402.

Funding information
Roche

Abstract

Background: Patients with haemophilic arthropathy suffer chronic pain that affects and restricts their quality of life. Visualization of movement through immersive virtual reality is used for pain management.

Aim: To evaluate the efficacy of 180-degree immersive VR motion visualization therapy in patients with haemophilic ankle arthropathy.

Methods: Prospective, multicentre pilot study. Fifteen adult patients with bilateral haemophilic ankle arthropathy were recruited (mean age: 42.73 ± 12.36 years). The intervention lasted 4 weeks, with daily home sessions of 180-degree immersive motion visualization. The patients were given virtual reality glasses to use with their smartphones. From the YouTube mobile app® they accessed the recorded video with access from the He-Mirror App®. The study variables were joint state (Haemophilia Joint Health Score), pressure pain threshold (pressure algometer), muscle strength (dynamometry) and range of motion (goniometry). Three evaluations were performed: at baseline (T0), after the intervention (T1) and at the end of a 16-week follow-up period (T2).

Results: No patient developed ankle hemarthrosis during the experimental phase. In the repeated measures analysis we found statistically significant differences in joint state ($F = 51.38$; $\eta^2_p = .63$), pressure pain threshold of the lateral malleolus ($F = 12.34$; $\eta^2_p = .29$) and range of motion ($F = 11.7$; $\eta^2_p = .28$).

Conclusions: Therapy using immersive motion visualization does not cause hemarthrosis. This intervention can improve joint condition, pressure pain threshold and range of motion in patients with ankle arthropathy. Changes greater than the MDC were reported in more than 40% of patients for the variables pressure pain threshold, anterior tibialis strength and range of motion, which were considered clinically relevant.

KEYWORDS
haemophilia, haemophilic ankle arthropathy, joint pain, range of motion, virtual reality exposure therapy

1 | INTRODUCTION

The recurrence of haemarthrosis in the same joint causes joint degeneration in patients with haemophilia.[1] One of the joints with the highest prevalence of haemophilic arthropathy is the ankle,[2] leading to chronic pain and a deteriorated quality of life.[3]

Chronic pain in patients with haemophilic arthropathy is highly prevalent. Pain intensity is usually moderate, sometimes reaching maximum peaks of severe pain.[4] Haemophilia patients suffering from chronic pain present catastrophism and kinesiophobia values comparable to those found in other chronic musculoskeletal pain populations. These values, in turn, reflect a poorer perception of quality of life.[4]

A recent study[5] discusses pain memory as a new concept to be considered in the treatment of haemophilia patients. As noted by Ucero-Lozano et al.,[4] painful experience is a possible modulator of the cognitive behavioural response in patients with haemophilia and chronic pain. However, this concept is not new in the physiotherapy approach to patients with chronic pain. More than 20 years ago, authors such as Gifford,[6] Moseley[7] or Hampton,[8] had already studied this concept in the physiotherapeutic treatment of chronic pain within a biopsychosocial approach. The concept, *"Pain is in the Brain"*, and the entire biopsychosocial model, is the basis of many of the treatments using cognitive behavioural approaches developed in patients with chronic pain. An example of these interventions are Vlaeyen's fear-avoidance model of pain,[9] the use of gradual exposure such as graduated motor imaging,[10] or the use of immersive visual reality in the treatment of pain.[11–13]

Chronic pain treatment in patients with haemophilia is based on the administration of analgesic or anti-inflammatory drugs.[14,15] The physiotherapy approach has focused on treating the tissue[3,14] through manual therapy and therapeutic exercise, or the use of ultrasound or pulsed magnetic field therapy.

Therapy using movement observation is a technique which is neurophysiologically based on mirror neurons and their activation when viewing the performance of a given action or one that is similar .[16,17] By observing movement, the motor system is activated in a similar way to the active execution of the observed action.[17] This phenomenon can be used to elicit neuroplastic changes. Movement observation is more effective when the video to be viewed is recorded from a first-person perspective and immersively.[18,19]

Treatment using immersive virtual reality (VR) with motion visualization has shown its effectiveness in reducing the perceived pain and pressure pain threshold in healthy subjects due to the action of the endogenous descending inhibitory systems.[20]

A recent review[21] has pointed out the possible effect of VR-based interventions on pain management, range of motion and proprioception in patients with knee and hip osteoarthritis. This effect is due to the neuroplastic changes in the brain caused by VR.[21]

The aim of the study was to evaluate the changes in joint condition, pressure pain threshold, strength and range of motion, after an immersive virtual reality intervention in patients with haemophilic ankle arthropathy.

2 | METHODS

2.1 | Study design

Prospective, multicentre pilot study.

2.2 | Patient recruitment and selection

Patients with haemophilia were recruited from the Spanish Federation of Haemophilia between September 2021 and January 2022.

The inclusion criteria of the study were (i) patients with a diagnosis of haemophilia A and B; (ii) with severe haemophilia phenotype (< 1% of FVIII/FIX); (iii) over 18 years of age; (iv) with haemophilic ankle arthropathy (more than 3 points on the *Haemophilia Joint Health Score*)[22]; and (v) having signed the informed consent document. Patients excluded from the study were those who (i) developed hemarthrosis during the study period; (ii) had neurological or cognitive disorders that impaired the understanding of the questionnaires and assessment tests; (iii) patients without pain in the ankle joint; (iv) amputee patients, with epilepsy or severe vision problems that prevent proper movement viewing on the mobile application; and (v) those patients receiving physical therapy treatment at the time of the study.

The development of antibodies to FVIII concentrates or the type of pharmacological treatment (prophylactic or on demand) were not included in the selection criteria.

2.3 | Ethical considerations

The main researcher informed the participants verbally and with an information sheet, about the possible risks and benefits of the study. All participants signed the Informed Consent Document. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Clinical Research Ethics Committee of the Virgen de la Arrixaca University Hospital (ID: 2020-2-9-HCUVA). Prior to the recruitment of patients, the research project was registered (www.clinicaltrials.gov; ID: NCT04549402).

2.4 | Measurement instruments

Before the experimental session, the main clinical variables (type of treatment, ankle joint condition, development of inhibitors) and anthropometric variables (weight and height) of the patients recruited in the study were collected.

All assessments were performed by a physiotherapist blinded to the study objectives. Three evaluations were performed: at baseline or pre-treatment (T0), at the end of the intervention (T1) and after the 16-week follow-up period (T2). The primary variable was the joint state of the ankle. The pressure pain threshold, gastrocnemius and tibialis anterior muscle strength, and range of motion were the secondary variables.

The joint condition was evaluated using the *Haemophilia Joint Health Score*.[23] This scale, specific for use in patients with haemophilia, evaluates eight items: *swelling* and *duration of swelling*, *pain*, *atrophy* and *muscle strength*, *crepitus*, and *loss of flexion* and *extension*. It is used in the evaluation of knees, ankles and elbows. The use of the Haemophilia Joint Health Score in clinical practice for the evaluation of paediatric and young adult patients with haemophilia has been widely analyzed.[24] Recently, a multicentre study has evidenced that this instrument provides high internal reliability in the assessment of arthropathy in adult patients with haemophilia (Cronbach's $\alpha = .88$).[25] The score ranges from 0 (no joint damage) to 20 points (maximum joint damage) per joint. In this study, only the ankle joint condition was evaluated (range 0–20).

By means of a pressure algometer (Wagner FDIX model, Wagner Instruments, CT, USA) the pressure pain threshold was assessed.[26] Bilateral and caudal pressure was exerted on the lateral malleolus and the medial malleolus[27] The pressure exerted by the evaluator gradually increased at an approximate speed of 50 kPa/s until the patient felt that the sensation was beginning to be painful.[28] The pressure algometer to assess the pressure pain threshold (PPT) is considered as a reliable and valid instrument to assess pain threshold (ICC = .91)[29] and, therefore, the subject's sensitivity to a nociceptive stimulus. The unit of measurement was Newton/cm^2.

Muscle strength was measured with a pressure dynamometer (Lafayette Manual Muscle Tester 01165).[30] The patient was placed in a supine position with his foot at 90° dorsal flexion.[31,32] The patient was asked to conduct two 5-s maximum isometric contractions, with a 30-s break in between, against the dynamometer held by the evaluator.[31,32] For the evaluation of the gastrocnemius strength, the dynamometer was placed proximal to the metatarsophalangeal joints on the plantar side. To assess the strength of the tibialis anterior, the dynamometer was placed proximal to the metatarsophalangeal joints on the dorsal side. The measurement of the strength of all the muscles evaluated uses the average value of both measurements as the measure.[28] Strength assessment with a pressure dynamometer has shown high interobserver reliability (ICC: .93–.98).[32] The higher the value, the greater the muscle strength. The unit of measurement was Newton.

To measure the ankle joint range of movement, a goniometric measurement was taken. The patient was placed in a supine position and with his knees slightly flexed, and his foot off the stretcher. The axis of the goniometer was placed on the lateral side of the lateral malleolus, the fixed arm aligned with the fibula and the mobile arm parallel to the fifth metatarsal.[31] Goniometric assessment of ankle range of motion has shown high interobserver reliability (ICC: .85–.96).[33] The unit of measurement employed is the degree, whereby the higher the degrees, the greater the range of motion.

Before beginning the study, an intraobserver reliability pilot test of the study variables was carried out. Reliability was evaluated for all study variables. Six patients with haemophilia, not included in the study, were evaluated on two consecutive days. There was high intraobserver reliability for joint state (intraclass correlation coefficient [ICC] = .981), range of motion (ICC = .96) and gastrocnemius strength (ICC = .945). Measurement of the tibialis anterior strength (ICC = .834) and the pressure pain threshold in the lateral (ICC = .882) and medial malleolus (ICC = .894), showed a moderate-high intraobserver reliability.

2.5 | Intervention

The intervention consisted of viewing the dorsal and plantar flexion movement of the ankle. A 180-degree immersive video in first-person perspective was used. The video was hosted on YouTube® with access from the He-Mirror App®, designed for this study by the research group. Patients viewed on their smartphones, regardless of the operating system, the immersive video while wearing virtual reality glasses (3D virtual reality glasses with remote control; model Q-MAX).[19] The patients had to be seated in a chair, with their feet relaxed and only resting on their heels. The intervention was performed at home on 28 consecutive days. Each session was 15 min long. During each session, patients had to watch the movement of both ankles on the video, without imagining the movement or performing it. Figure 1 shows the intervention as performed by one of the patients included in the study.

2.6 | Sample size

The sample size was calculated using the statistical package G * Power (version 3.1.9.2; Heinrich-Heine-Universität Düsseldorf, Germany). Assuming a large effect size (d = .80), with an alpha level (type I error) of .05 and a statistical power of 80% (1-β = .80), a sample size of 12 patients was estimated. Due to the forecast of dropouts during the experimental phase and the follow-up period, 15 patients with haemophilia and ankle arthropathy were recruited. The mean age of the patients was 42.73 (SD: 12.36) years. The majority of patients were diagnosed with haemophilia A (80%) and were undergoing on-demand treatment (53.3%). All patients had a severe disease phenotype (< 1% FVIII/FIX) and only three patients had antibodies to clotting factor concentrates (inhibitors).

During the study period, none of the patients included in the study developed hemarthrosis as a result of the intervention. One of the study patients was excluded due to failure to adhere to the

FIGURE 1 Patient performing the intervention of 180-degree immersive VR motion visualization

TABLE 1 Descriptive characteristics of patients with haemophilic ankle arthropathy at baseline

Variables		Mean (standard deviations)
Age (years)		42.73 (12.36)
Weight (kg)		81.07 (10.77)
Height (cm)		173.27 (7.52)
Body Mass Index (Kg/m^2)		27.01 (3.27)
		***n* (%)**
Type of haemophilia		
	A	12 (80)
	B	3 (20)
Treatment		
	Prophylactic	7 (46.7)
	On demand	8 (53.3)
Inhibitors		
	Yes	3 (20)
	No	12 (80)

intervention (64% of the sessions), although this patient was included in the intention-to-treat analysis. Another patient dropped out of the study due to eye problems following trauma. The descriptive characteristics of the patients included in the study are shown in Table 1.

2.7 | Statistical analysis

Data analyses were performed using the statistical package SPSS for Windows, version 19.0, (IBM Company, Armonk, NY, USA). Intraobserver reliability was calculated using the intra-class correlation coefficient. Statistics of central tendency and dispersion (mean and standard deviation) of the study variables were calculated. The within-subject effect was calculated using the repeated measures ANOVA. The partial eta-squared value (η^2_p) was calculated as an indicator of the effect size, classified as small (.01), medium (.06) or large (.14).[34]

The minimum detectable change (MDC) was calculated by estimating the standard error of measurement (SEM). The SEM was calculated with the formula: SEM = $SD_{pre} * \sqrt{1}$-intraclass correlation coefficient (ICC).[35] Based on SEM, the MDC was obtained (MDC = Z-score $* \sqrt{2} *$ SEM). The confidence level was set at 95% (Z score = 1.96).[36] The proportion of patients whose change exceeded the MDC was calculated. An intent-to-treat analysis was performed to analyse the results. The selected significance level was .025 ($\alpha = .05 / 2$).

3 | RESULTS

At the end of the intervention and the follow-up period, we found within-subject differences ($p < .025$) in the variables joint status (F(1.45; 42.14) = 51.38), pressure pain threshold in the lateral malleolus (F(2;58) = 12.34) and range of motion (F(2;58) = 11.7). High effect size was noted for the variables joint health ($\eta^2_p = .63$), external malleolus pressure pain threshold ($\eta^2_p = .29$), tibialis anterior strength ($\eta^2_p = .12$) and range of motion ($\eta^2_p = .28$). Table 2 shows the central tendency and dispersion statistics, and the repeated measures analysis.

After the intervention there were significant changes in the variables joint health ($p < .001$), external malleolus pressure pain threshold ($p = .001$), tibialis anterior strength ($p = .007$) and range of motion ($p < .001$). When comparing the initial and follow-up evaluations, there were statistically significant differences in the variables joint health ($p < .001$), external malleolus pressure pain threshold (p = .004), and range of motion ($p = .009$). Table 3 shows the pairwise comparison analysis.

At the end of the study period, 46% of the patients showed an improvement greater than the minimum detectable change (6035) calculated for the lateral malleolus pain threshold (from 39.39 to 46.38 after the intervention). The improvement in range of motion (from 33.20 to 36.47) was greater than the minimum detectable change (3.921) in 40% of the patients. With regard to joint condition, 36.66% of the patients showed changes (from 12.07 to 10.87) beyond the minimum detectable change calculated (1.829). Table 4 shows the analyses of the minimum detectable change.

4 | DISCUSSION

The aim of the study was to evaluate the changes in joint condition, pressure pain threshold, joint strength and range of motion, after an

TABLE 2 Means (and standard deviations) and within-subject results in each one of the dependent variables of the study for the study groups

Variables	T0	T1	T2	W	F	η^2_p
Joint health (0–20)	12.07 (2.65)	10.87 (2.28)	11.10 (2.35)	.62†	51.37**	.63
External malleolus pressure pain threshold (Kg/cm^2)	39.39 (14.23)	46.38 (14.12)	45.04 (14.02)	.89	12.34**	.29
Internal malleolus pressure pain threshold (Kg/cm^2)	43.64 (13.75)	45.87 (13.04)	45.87 (12.46)	.93	3.51	.10
Gastrocnemius strength (N)	283.81 (70.27)	288.20 (70.75)	284.30 (70.21)	.91	3.08	.09
Tibialis anterior strength (N)	216.88 (55.69)	224.95 (58.28)	220.32 (52.51)	.70†	4.31	.12
Range of motion (degrees)	33.20 (15.82)	36.47 (15.79)	35.20 (15.59)	.96	11.70*	.28

Outcome measures at baseline (T0), after the 4-week period of interventions (T1) and after 16-week period of follow-up; W: Mauchly's Sphericity Test; η^2_p: partial Eta-squared.
†The df corresponds to Greenhouse–Geisser test.
*Significant difference between assessments ($p < .025$).
**Significant difference between assessments ($p < .001$).

TABLE 3 Pairwise comparison analysis, mean difference (and 95% confidence interval), between the assessments

	T0 – T1		T0 – T2	
Variables	MD	95%CI	MD	95%CI
Joint health	1,20**	.82 – 1.57	.96**	.61 – 1.32
External malleolus pressure pain threshold	−6.98*	−11.14 – −2.83	−5.65*	−9.67 – −1.62
Internal malleolus pressure pain threshold	−2.23	−4.41 – −.06	−2.23	−4.96 – .50
Gastrocnemius strength	−4.39	−5.91 – 4.93	−.49	−5.91 – 4.93
Tibialis anterior strength	−8.07*	−14.25 – −1.88	−3.43	−9.22 – 2.35
Range of motion	−3.26**	−5.12 – −1.40	−2.00*	−3.56 – −.44

T0 – T1: outcome measures for baseline to posttreatment assessments; T0 – T2: outcome measures for baseline to follow-up assessments; MD: mean differences; 95%CI: 95% confidence interval.
*Significant difference between assessments ($p < .025$).
**Significant difference between assessments ($p < .001$).

TABLE 4 Minimal detectable change of joint status, joint pain, range of motion and hamstring flexibility evaluated in the different assessments

Variables	ICC	SEM	MDC (MDCp)
Joint health	.973	.435	1.829 (36.66)
External malleolus pressure pain threshold	.889	4.740	6.035 (46.66)
Internal maleolus pressure pain threshold	.968	2.459	4.347 (30.0)
Gastrocnemius strength	.994	5.444	6.46 (33.33)
Tibialis anterior strength	.986	6.589	7.115 (53.33)
Range of motion	.984	2.001	3.921 (40.0)

Abbreviation: ICC, intra-rater intraclass correlation coefficient; SEM, standard error of measurement; MDC, minimal detectable change; MDCp, proportion of minimal detectable change.

immersive virtual reality intervention in patients with haemophilic ankle arthropathy. At the end of the intervention improvements were found in joint condition, pressure pain threshold of the lateral malleolus and range of motion. The treatment using immersive reality did not cause ankle hemarthrosis during the intervention period.

Treatment using movement observation can improve joint condition in patients with ankle arthropathy. The *Haemophilia Joint Health Score* evaluates the joint condition in patients with haemophilia based on items which greatly improved in our study. The increase in pressure pain threshold and range of motion are the main causes of such joint

improvement. Davari et al[37] noted how the change in the joint health score is related to a better perception of quality of life in patients with haemophilia. Although our study did not evaluate the quality of life of our patients, the significant change with a high effect size observed may represent a future line of work in the management of these patients.

Krüger et al.[38] noted how the pain profile in patients with haemophilia does not change over time. However, changes observed in the pressure pain threshold in our study may be mediated by descending inhibitory pathways. This may be due to the fact that the same cortical areas activated during movement execution are also activated when observing the movement. In this way, cortical excitability increases, which is associated with a decrease in pain perception[39] The changes reported in our study are consistent with those observed by Morales Tejera et al.[39] when applying observation of movement in asymptomatic adult subjects without cervical pain. The increased pressure pain threshold during movement visualization is consistent with the results of a recent study where a 8-week self-induced myofascial release intervention rendered changes in the pain threshold of patients with knee arthropathy.[40]

Physiotherapy techniques in which a mechanical effect is applied, such as self-induced myofascial release with a Foam Roller[40] and manual therapy,[41] have shown to be effective in improving the range of motion in patients with haemophilic knee and elbow arthropathy. The increased ankle range of motion reported in our study using immersive virtual reality may be due to the neurophysiological effect associated with the activation of cortical areas.[17] The reduction in fear-avoidance behaviours as described by Vlaeyen et al.[9] could be due to the creation of an illusory image of a healthy limb while observing the action.[21] A study on patients with total knee arthroplasty disclosed an improvement in range of motion of the knee after a 10-day intervention using motion visualization.[42]

Visualization of movement can improve quadriceps muscle activation in patients with knee arthropathy.[43] However, none of the studies have disclosed significant changes in muscle strength after a motion observation intervention. The improvement in muscle strength depends on the generation of changes in the load or in the maximum speed of movement execution.[44]

More than 40% of patients in our study reported an improvement exceeding the MDC in pressure pain threshold on the external malleolus, tibialis anterior muscle strength and range of motion. These values, although lower than those observed in other studies[45] should be interpreted from a clinical perspective. This intervention based on visualization of movement causes changes due to brain modulation. Similarly, the high effect size values observed for the variables external malleolus pressure pain threshold, range of motion and joint health should be highlighted. Despite the small sample size, these values may indicate the clinical relevance of this technique in the management of patients with haemophilic ankle arthropathy.

4.1 | Limitations of the study

This study presents several limitations to be accounted for. The study design as a cohort study limits the interpretation of the results. This study has not registered the intake of analgesic drugs that could bias the results, especially with regard to the pressure pain threshold. The absence of an evaluation of functionality prevents us from establishing the real impact of immersive movement visualization.

4.2 | Recommendations for future research

Future studies should confirm the results reported for an intervention using immersive motion visualization. Randomized, multicentre clinical studies are essential to implement the effectiveness of this intervention. The inclusion of functionality and psychosocial variables would allow us to establish the global impact of immersive movement visualization for patients with haemophilic arthropathy. Pain assessment with different measuring instruments would make it possible to distinguish between the changes in pain intensity, pain threshold and inhibitory control.

5 | CONCLUSIONS

Therapy using 180-degree immersive VR motion visualization is safe in patients with haemophilia. This intervention can improve joint condition, pressure pain threshold and mobility in patients with haemophilic ankle arthropathy. Changes greater than the MDC obtained in external malleolus pressure pain threshold, tibialis anterior strength, and range of motion could be considered clinically relevant and used to evaluate the effect of motion visualization in patients with haemophilic arthropathy. Randomized clinical studies are needed to confirm the findings of this study and the efficacy of immersive movement visualization.

ACKNOWLEDGEMENTS

We would like to thank the patients and participants in this study for taking the time to participate in the assessments and the patient associations for helping with sample recruitment. We acknowledge the grant from Roche Farma, S.A. The funders played no role in the design, conduct, or reporting of this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Rubén Cuesta-Barriuso https://orcid.org/0000-0002-4276-6982

REFERENCES

1. Knobe K, Berntorp E. Haemophilia and joint disease: pathophysiology, evaluation, and management. *J Comorbidity*. 2011;1(1):51-59.
2. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1-47.
3. Visweshwar N, Zhang Y, Joseph H, et al. Chronic pain in patients with hemophilia: is it preventable? *Blood Coagul Fibrinolysis Int J Haemost Thromb*. 2020;31(6):346-352.
4. Ucero-Lozano R, López-Pina JA, Ortiz-Pérez A, Cuesta-Barriuso R. The relationship between chronic pain and psychosocial aspects in patients with haemophilic arthropathy. A cross-sectional study. *Haemophilia*. 2022;28(1):176-182.
5. Wells AJ, Whitaker S, Gray D, et al. Pain memories: a new concept to consider in the management of chronic pain in people with haemophilia. *Haemophilia*. 2022;28(2):e46-e48.
6. Pain, the tissues and the nervous system: a conceptual model. *Physiotherapy*. 1998;84(1):27-36.
7. Moseley GL. A pain neuromatrix approach to patients with chronic pain. *Man Ther*. 2003;8(3):130-140.
8. Pain and the brain: researchers focus on tackling pain memories. *JAMA*. 2005;293(23):2845-2846.
9. Behavioral conceptualization and treatment of chronic pain. *Annu Rev Clin Psychol*. 2020;16(1):187-212.
10. The effects of graded motor imagery and its components on chronic pain: a systematic review and meta-analysis. *J Pain*. 2013;14(1):3-13.
11. Hoffman HG, Boe DA, Rombokas E, et al. Virtual reality hand therapy: a new tool for nonopioid analgesia for acute procedural pain, hand rehabilitation, and VR embodiment therapy for phantom limb pain. *J Hand Ther Off J Am Soc Hand Ther*. 2020;33(2):254-262.
12. Putrino D, Tabacof L, Breyman E, et al. Pain reduction after short exposure to virtual reality environments in people with spinal cord injury. *Int J Environ Res Public Health*. 2021;18(17):8923.
13. Czub M, Piskorz J, Misiewicz M, et al. Influence of memory on experienced pain during virtual reality analgesia. *Pol J Appl Psychol*. 2014;12(4):41-52.
14. Rodriguez-Merchan EC. Treatment of musculo-skeletal pain in haemophilia. *Blood Rev*. 2018;32(2):116-121.
15. Tagliaferri A, Franchini M, Rivolta GF, et al. Pain assessment and management in haemophilia: a survey among Italian patients and specialist physicians. *Haemophilia*. 2018;24(5):766-773.
16. Öztürk Ö, Bombacı H, Keçeci T, et al. Effects of additional action observation to an exercise program in patients with chronic pain due to knee osteoarthritis: a randomized-controlled trial. *Musculoskelet Sci Pract*. 2021;52:102334.
17. Action observation treatment: a novel tool in neurorehabilitation. *Philos Trans R Soc Lond B Biol Sci*. 2014;369(1644):20130185.
18. Virtual reality-based action observation facilitates the acquisition of body-powered prosthetic control skills. *J Neuroengineering Rehabil*. 2020;17(1):113.
19. Choi JW, Kim BH, Huh S, et al. Observing actions through immersive virtual reality enhances motor imagery training. *IEEE Trans Neural Syst Rehabil Eng Publ IEEE Eng Med Biol Soc*. 2020;28(7):1614-1622.
20. Hayashi K, Aono S, Shiro Y, et al. Effects of virtual reality-based exercise imagery on pain in healthy individuals. *BioMed Res Int*. 2019;2019:1-9.
21. Byra J, Czernicki K. The effectiveness of virtual reality rehabilitation in patients with knee and hip osteoarthritis. *J Clin Med*. 2020;9(8):E2639.
22. Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. *Haemophilia*. 2006;12(5):518-525.
23. Fischer K, Kleijn P de. Using the Haemophilia Joint Health Score for assessment of teenagers and young adults: exploring reliability and validity. *Haemophilia*. 2013;19(6):944-950.
24. Feldman BM, Funk SM, Bergstrom B-M, et al. Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: validity of the hemophilia joint health score. *Arthritis Care Res*. 2011;63(2):223-230.
25. St-Louis J, Abad A, Funk S, et al. The hemophilia joint health score version 2.1 validation in adult patients study: a multicenter international study. *Res Pract Thromb Haemost*. 2022;6(2):e12690.
26. Examination of muscle strength and pressure pain thresholds in knee osteoarthritis: test-retest reliability and agreement. *J Geriatr Phys Ther*. 2015;38(3):141-147.
27. Plaza-Manzano G, Vergara-Vila M, Val-Otero S, et al. Manual therapy in joint and nerve structures combined with exercises in the treatment of recurrent ankle sprains: a randomized, controlled trial. *Man Ther*. 2016;26:141-149.
28. Somatosensory perception and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from rheumatoid arthritis. *Eur J Pain*. 2002;6(2):161-176.
29. Chesterton LS, Sim J, Wright CC, et al. Interrater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. *Clin J Pain*. 2007;23(9):760-766.
30. Pfister P, de Bruin ED, Sterkele I. Manual muscle testing and hand-held dynamometry in people with inflammatory myopathy: an intra- and interrater reliability and validity study. *PLOS ONE*. 2018;13(3):e0194531.
31. Tat NM, Can F, Sasmaz HI, et al. The effects of manual therapy on musculoskeletal system, functional level, joint health and kinesiophobia in young adults with severe haemophilia: a randomized pilot study. *Haemophilia*. 2021;27(2):e230-38.
32. Andrews AW, Thomas MW, Bohannon RW. Normative values for isometric muscle force measurements obtained with hand-held dynamometers. *Phys Ther*. 1996;76(3):248-259.
33. Konor MM, Morton S, Eckerson JM, et al. Reliability of three measures of ankle dorsiflexion range of motion. *Int J Sports Phys Ther*. 2012;7(3):279-287.
34. Pallant J, SPSS Survival Manual. 6th ed. Maidenhead New York: Open University Press; 2016.
35. Schmitt JS, Di Fabio RP. Reliable change and minimum important difference (MID) proportions facilitated group responsiveness comparisons using individual threshold criteria. *J Clin Epidemiol*. 2004;57(10):1008-1018.
36. de Vet HC, Terwee CB, Ostelo RW, et al. Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change. *Health Qual Life Outcomes*. 2006;4:54.
37. Davari M, Gharibnaseri Z, Ravanbod R, et al. Health status and quality of life in patients with severe hemophilia A: a cross-sectional survey. *Hematol Rep*. 2019;11(2):7894.
38. Krüger S, Herzig M, Hilberg T. Changes in pain profile of patients with haemophilia during 1-year follow-up. *Haemoph Off J World Fed Hemoph*. 2021;27(5):783-792.
39. Morales Tejera D, Fernandez-Carnero J, Suso-Martí L, et al. Comparative study of observed actions, motor imagery and control therapeutic exercise on the conditioned pain modulation in the cervical spine: a randomized controlled trial. *Somatosens Mot Res*. 2020;37(3):138-148.
40. Pérez-Llanes R, Meroño-Gallut J, Donoso-Úbeda E, et al. Safety and effectiveness of fascial therapy in the treatment of adult patients with hemophilic elbow arthropathy: a pilot study. *Physiother Theory Pract*. 2020:1-10.
41. Cuesta-Barriuso R, Pérez-Llanes R, López-Pina JA, et al. Manual therapy reduces the frequency of clinical hemarthrosis and improves range of motion and perceived disability in patients with hemophilic elbow arthropathy. A randomized, single-blind, clinical trial. *Disabil Rehabil*. 2022;44(15):3938-3945.

42. Villafañe JH, Isgrò M, Borsatti M, et al. Effects of action observation treatment in recovery after total knee replacement: a prospective clinical trial. *Clin Rehabil*. 2017;31(3):361-368.
43. Ucero-Lozano R, Pérez-Llanes R, López-Pina JA, et al. One session effects of knee motion visualization using immersive virtual reality in patients with hemophilic arthropathy. *J Clin Med*. 2021;10(20):4725.
44. Galiano C, Pareja-Blanco F, Hidalgo de Mora J, et al. Low-velocity loss induces similar strength gains to moderate-velocity loss during resistance training. *J Strength Cond Res*. 2022;36(2):340-345.
45. Pérez-Llanes R, Donoso-Úbeda E, Meroño-Gallut J, et al. Safety and efficacy of a self-induced myofascial release protocol using a foam roller in patients with haemophilic knee arthropathy. *Haemoph Off J World Fed Hemoph*. 2022;28(2):326-333.

How to cite this article: Ucero-Lozano R, Pérez-Llanes R, López-Pina JA, Cuesta-Barriuso R. 180-degree immersive VR motion visualization in the treatment of haemophilic ankle arthropathy. *Haemophilia*. 2023;29:282–289.
https://doi.org/10.1111/hae.14683