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REVIEW ARTICLE

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Physiotherapy interventions for pain management in haemophilia: A systematic review

Paul McLaughlin[1,2] | Michael Hurley[1] | Pratima Chowdary[2] | Kate Khair[3] | David Stephensen[4]

[1]St George's University of London and Kingston University, London, UK

[2]Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Hospital, London, UK

[3]Centre for Outcomes and Experience Research in Child Health, Illness and Disability (ORCHID) Research Unit, Great Ormond Street Hospital for Children NHS Trust, London, UK

[4]East Kent Hospitals University NHS Foundation Trust, Kent, UK

Correspondence
Paul McLaughlin, Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, Pond St, London NW3 2QG, UK.
Email: p.mclaughlin@nhs.net

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Abstract

Purpose: Approximately 35%-50% of people with haemophilia (PWH) report living with chronic musculoskeletal pain. Although exercise based rehabilitation is effective for pain in other arthritises, there are no published guidelines for management of chronic pain in PWH. This review aims to evaluate and appraise the current evidence of effectiveness of physiotherapy interventions on (a) pain intensity, (b) quality of life (QoL) and (c) function in PWH.

Methods: A systematic review of five databases AMED and CINAHL, EMBASE and MEDLINE and PEDro, as well as trial registries, grey literature and hand searching key journals was completed. Included studies were critically appraised and evaluated for risk of bias. The GRADE approach was used to rate the quality of the evidence.

Results: Nine trials consisting of 235 participants met the inclusion criteria. All studies had an overall risk of bias with low methodological quality. Meta-analysis was not possible due to heterogeneity across trials. Studies comparing a range of physiotherapy interventions against no intervention showed no clear beneficial effect on pain intensity or QoL. Only one study, investigating hydrotherapy or land-based exercise against control, showed positive effect for pain intensity, but rated very low on GRADE assessment. Studies comparing one physiotherapy intervention against another showed no clear benefit on pain intensity, QoL or function. LASER with exercise and hydrotherapy were shown to have some positive effects on pain intensity, but no clear benefit on function.

Conclusions: At present, there is limited evidence for the use of physiotherapy interventions in addressing the issue of pain in PWH. Better designed trials with higher quality and explicit methodology along with user involvement are needed to assess the efficacy of any proposed intervention.

KEYWORDS

arthropathy, Haemophilia, pain management, physiotherapy

1 | INTRODUCTION

Haemophilia is an inherited bleeding disorder characterized by recurrent and spontaneous bleeding into joints and muscles and fatal bleeding in the untreated state.[1,2] People with haemophilia (PWH) experience transient episodes of acute pain from an early age from musculoskeletal bleeding episodes. Despite replacement therapy, some PWH continue to have bleeding into their joints and muscles, which can lead to debilitating arthritis with chronic and recurrent pain.[3]

People with haemophilia over the age of 65 had no access to regular treatment until they were in adulthood, with those currently aged in their 40's having no access to effective treatment for the majority of their childhood.[4] Consequently, many PWH have chronically painful, multi-joint haemophilic arthritis, involving elbow, knee and ankle joints.[5-7]

Between 35% and 50% of PWH report living with chronic musculoskeletal pain,[7-10] with 40% reporting their pain is poorly managed by their healthcare provider.[8] PWH living with pain report limitations in mobility and independence, increased anxiety, poor quality of life and frustration due to restrictions in activities of daily living.[7,11,12]

A recent systematic review of management of multisite osteoarthritis (OA) found that exercise interventions may have moderate benefits on pain, function and quality of life.[13] More specifically, aerobic exercise has been shown to be effective for pain management and functional improvements in rheumatoid arthritis[14] and in OA when used with mind-body interventions.[15] However, although pain is a widespread problem in haemophilia, there are no published guidelines for the physiotherapy of management of chronic arthritic joint pain in this population.

1.1 | Objective

This review aims to evaluate and appraise the current evidence of the effects of physiotherapy interventions on (a) pain intensity, (b) quality of life and (c) function in PWH.

2 | METHODS

2.1 | Protocol and registration

The protocol was registered with the International Prospective Register of Systematic reviews (PROSPERO number: CRD42018116482). Reporting is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16]

2.2 | Eligibility criteria

Study design for inclusion was those described as randomized controlled trials and quasi-experimental studies including controlled studies, before and after and interrupted time studies, comparing to no intervention/routine care group or between group comparison of one treatment intervention against another.

Studies describing any physiotherapy/rehabilitation/physical therapy intervention that had pain intensity, functional outcomes and health related quality of life as outcome measures were included.

Studies with participants of any age with a diagnosis of mild, moderate or severe haemophilia (A or B), and/or haemophilic arthritis were included. Those with participants with a diagnosis of an inhibitor (antibody to factor VIII or IX) and co-morbidities were not excluded. There was no restriction in country or care settings for studies.

Studies that investigated joint disease or pain as a result other inherited bleeding disorders such as von Willebrand disease were excluded.

2.3 | Information sources

A systematic search of the literature was conducted from the date of database conception to 20/07/2018, with a follow-up search again on 07/09/2018 (PML). The approaches used were as follows:

1. AMED (EBSCO), CINAHL (EBSCO), EMBASE (OVID), MEDLINE (OVID) and PEDro
2. Cochrane central register of controlled trials
3. Trial registries—clinicaltrial.gov, international trials registry, EU clinical trials register
4. Grey literature
5. Hand searching key journals
6. Checking reference lists of previous related systematic reviews in haemophilia
7. Hand searched abstract book of EAHAD congress (European Association of Haemophilia and Associated Disorders) 2000-2018 and WFH (World Federation of Haemophilia) world congresses 2000-2018

Only studies published in the English language were included.

2.4 | Search strategy

Figure 1 details the search strategy used across each database. Iterative refinement of the search strategy was achieved after multiple practice searches using potential search terms and associated subject headings. The university version of OVID and EBSCO search platforms maps to subject headings by default. The search strategy was discussed in detail and endorsed by the University librarian (AE-J).

2.5 | Study selection

One reviewer (PML) independently carried out the search strategy on the listed databases. Results were saved, duplicates removed and

FIGURE 1 Search strategy of terms for all databases [Colour figure can be viewed at wileyonlinelibrary.com]

Database/register	Search years	Search terms
AMED (EBSCO)	1985- present	#H(a)emophilia AND physio*/ physical*-therapy
CINAHL (EBSCO)	1961- present	#H(a)emophilia AND physio*/ physical*-therapy
EMBASE (OVID)	1976- present	#1 exp h*emophilia #2 exp pain #3 1 AND 2 #4 exp physio*/physical*-therapy #5 exp manual therapy or exp manipulative medicine #6 exp hydrotherapy or exp "aquatic exercise" #7 exp electrotherapy or exp "electrophysical agents" #8 exp rehabilitation or "home rehabilitation" or "rehabilitation medicine" or "exercise supervised" or "exercise unsupervised" #9 exp "patient education" #10 4 or 5 or 6 or 7 or 8 or 9 #11 3 AND 10 #12 "randomi*ed controlled trial" or "controlled trial" or randomi*ed #13 11 AND 12 (filter limits Full Text and English Language)
MEDLINE (OVID)	1964- present	
PEDro		#H(a)emophilia
www.clinicaltrials.gov		#H(a)emophilia AND physio*/ physical*-therapy
International Trials registry http://apps.who.int/trialsearch/		#H(a)emophilia AND physio*/ physical*-therapy
EU Clinical Trials Register www.clinicaltrialsregister.eu		#H(a)emophilia AND physio*/ physical*-therapy

then imported to the Rayyan platform,[17] enabling two reviewers (PML, DS) to independently review titles and abstracts whilst blinded from each other. Once each reviewer had completed their check, the abstracts were unblinded. We compared those which had been accepted, rejected and were undecided by both reviewers, and discrepancies between reviewers (n = 2) were discussed and a consensus reached.

Full texts of agreed abstracts were retrieved and evaluated independently (PML, DS) to determine eligibility for inclusion in the systematic review.

2.6 | Data collection process

A data extraction proforma was developed using the Cochrane Airways group template (https://airways.cochrane.org/data-collection). One reviewer (PML) extracted data studies, and a second reviewer (DS) checked extracted data for accuracy. One author was contacted for further information, and data were received.[18]

2.7 | Data items

Information extracted from each trial included study design, participant information, interventions, comparison interventions, outcome measures (pre- and postintervention, follow-up if available), results including pain, function and quality of life.

2.8 | Risk of bias in individual studies

The Cochrane Risk of Bias assessment tool was used to assess included papers and was carried out independently by two authors (PML, DS). Criteria of unclear, low or high risk of bias were assigned against selection bias, performance bias, detection bias, attrition bias, reporting bias and any other identified bias.

2.9 | Methods of analysis

Cochrane collaboration software (RevMan version 5.3)[19] was used to collate and analyse study data.

Mean change from baseline to follow-up and standard deviation of mean difference (MD) was calculated for input into RevMan. Using a fixed effects model, mean differences ± 95% confidence interval (CI) per intervention were calculated. Studies were grouped into (a) physiotherapy intervention vs no intervention and (b) physiotherapy intervention A vs physiotherapy intervention B.

A narrative synthesis of the evidence was completed including the use of the GRADE approach in grading evidence quality.[20] The GRADE system uses eight criteria against which to assess the quality of evidence as either high, moderate, low or very low. They are (a) risk of bias, (b) inconsistency, (c) indirectness, (d) imprecision, (e) publication and (f) other (i. large effect, ii. dose response, iii. no plausible confounding—only these assessments permit an upgrade). All outcomes start on 'high' quality (those studies not an RCT start score

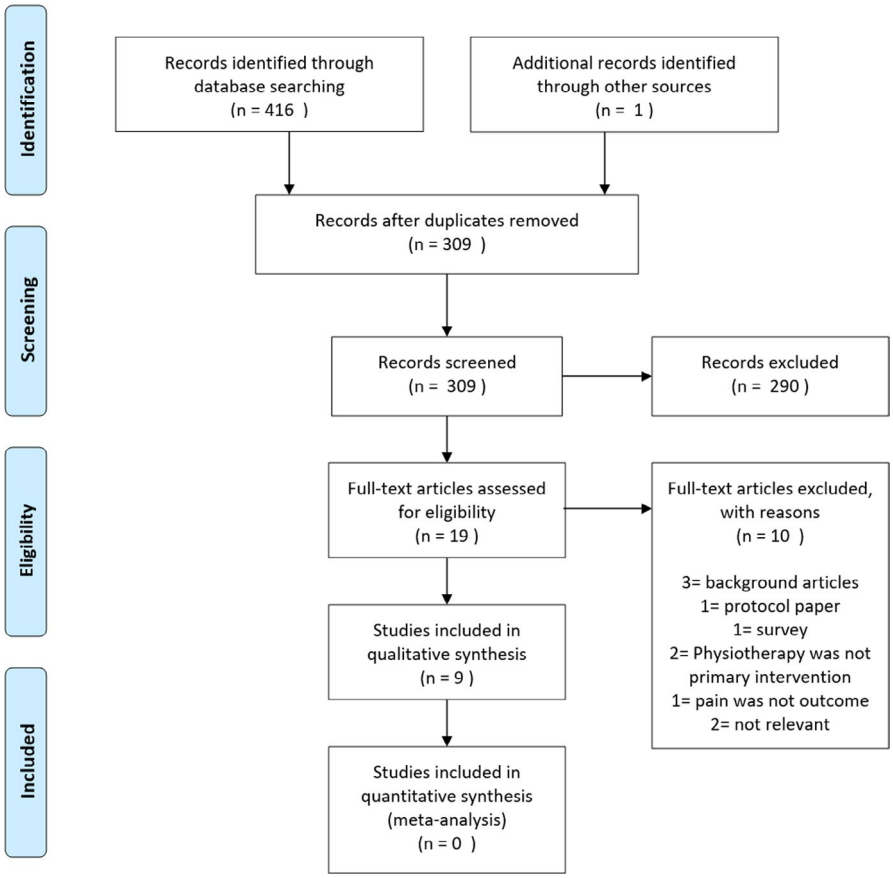

FIGURE 2 Flow chart of trial identification and selection for inclusion in review [Colour figure can be viewed at wileyonlinelibrary.com]

process on 'low'). They may then be downgraded one level per criteria if it is deemed to have a serious risk (−1) or very serious risk (−2).[21]

2.10 | Additional analysis

We were unable to undertake meta-analysis due to heterogeneity of the included studies.

3 | RESULTS

3.1 | Study selection

The search strategy identified 417 citations. Following removal of duplicates, 309 remained. Review of abstracts resulted in removal of 290, with further 10 being removed after full text review (Figure 2).

3.2 | Study characteristics

Nine studies were identified (Table 1). The number of participants per study ranged from 9[22] to 40.[23] The number of participants across all studies was 235. Of these, 60 were children (aged 9-13) and 175 were adults (aged 26-58). Severity of haemophilia was not specified for 70 participants. Of the remaining 165, 93 were identified as having a diagnosis of severe haemophilia, 50 moderate, 17 mild and 5 mild/moderate. One hundred and forty-nine participants were on prophylaxis and 46 were on-demand. Treatment regime was not stated for 40 people. Following GRADE assessment, all nine studies were rated as low/very low for quality of evidence.

3.3 | Interventions

Study intervention periods ranged from 3 to 15 weeks. Four trials had a RCT design.[18,23-25]

Four studies compared one physiotherapy intervention against another: passive joint mobilizations and exercise vs manual therapy and exercises in adults with haemophilic ankle arthropathy[22]; high intensity laser therapy (HILT) and exercise vs pulsed electromagnetic field and exercise in treatment of knee haemarthrosis in children[26]; home exercise programme and self-monitoring vs home exercise alone for haemophilic in adults with knee and ankle arthropathy[27]; and HILT and exercise vs placebo HILT and exercise in haemophilic arthropathy of the knee in children.[28]

Three studies in adults compared two physiotherapy intervention arms against a control group; manual therapy and exercise against patient education and exercise in haemophilic ankle

arthropathy,[24] with the same study design replicated for elbow arthropathy.[18] A third study investigated hydrotherapy against land-based exercise with a control group in haemophilic knee arthropathy.[23]

Two studies in adults compared one physiotherapy intervention with a control group; patient education and home exercises verses control on elbow, knee and ankle haemophilic arthropathy[25]; and fascial therapy vs control on knee and ankle haemophilic arthropathy.[29]

One study performed the intervention 3 sessions per week for 3 weeks,[29] with another not stating how many sessions were performed over 4 weeks.[23] Two studies performed the intervention for 2 sessions per week for 6 weeks,[18,22] and one study encouraged participants to do exercises 10 times a day for 8 weeks.[27] Another performed 2 sessions per week over 12 weeks[24] with another doing 1 session every 2 weeks for 12 weeks.[18] The participants in two studies received 3 sessions per week for 12 weeks[26] and another one session every 2 weeks for 15 weeks.[25]

3.4 | Risk of bias

All studies had an overall risk of bias (see Figure 3). Assessment of risk of bias found agreement between study authors was moderate (Cohen's *K* 0.51).

3.4.1 | Sequence generation

One study rated low risk as it described the use of a random number generation table for each participant.[27] Six studies were rated as unclear risk as sequence generation methods were not described. One paper rated high risk as participants were chosen for inclusion based on geographical location.[29]

3.4.2 | Allocation concealment

Two studies had a low risk with both describing opaque envelopes being distributed by someone unrelated to the study.[18,25] Six studies were rated unclear due to lack of detail on methods of concealment. One study rated high risk as participants were selected based on geography.[29]

3.4.3 | Blinding

Blinding of the participants was not possible in any of the included studies, and none of personnel were blinded in any study. Five studies used blinded evaluators to assess outcomes[18,22,24-26] and were rated low risk. Two studies rated unclear as they did not state if outcome assessment was blinded,[23,28] and two rated high risk as outcome assessment was completed by the same individuals delivering the intervention.[27,29]

3.4.4 | Incomplete outcome data

Four studies rated as low risk of attrition bias because each stated that all participants completed the intervention.[18,22,25,27] Five rated unclear as although they did not report dropouts, they also did not explicitly state that all had completed the intervention.[18,24,26,28,29] One study was rated high risk as although the authors reported three dropouts, they did not specify from which group they came.[23]

3.4.5 | Selective reporting

Three studies were rated high risk of selective reporting bias. One study failed to report on changes to bleeding frequency even though this was an inclusion criteria for the study.[26] Another describes an improvement in joint health with the Haemophilia Joint Health Score but include no data to support this[28] and another does not report on all of the elbow joints included in their study.[18] The six other studies had unclear risk of selective reporting bias.

No study was determined to have any source of other potential bias and therefore were rated as low.

3.5 | Data synthesis

Outcome measures for the nine trials are presented in Table 1. Although there were multiple outcomes measured across the trials, for the purposes of this review only those of pain intensity, quality of life and functional capability are included in this qualitative analysis, as per our protocol.

Data presented apply only to immediate postintervention assessments. All nine studies included an assessment for pain using the visual analogue scale (VAS). Two trials assessed health related quality of life (HR-QoL) using the A36 Haemophilia-QOL questionnaire.[22,25] Physical function was assessed in three studies using the 6-minute walk test (6MWT),[26] the 10 meter walk test (10MWT) and a modified functional reach test another.[27] No other studies measured function or HR-QoL.

Where trials compared two physiotherapy interventions against a control, results from each intervention were analysed individually against the control (physiotherapy intervention vs no intervention), as well as against each other (A vs B).

4 | PHYSIOTHERAPY VS NO INTERVENTION

Five studies were included in this comparison (Figure 4).[18,23-25,29]

TABLE 1 Summary of included studies with GRADE assessment

Trial and location	Methods	Participants	Intervention
Cuesta-Barriuso 2014[22] (Spain)	Quasi-experimental pre-post design	9 Adults with haemophilia A or B (mean age 35.8) and arthropathy in one or both ankles on prophylaxis. 3 bilateral ankle arthropathy, 5 with right ankle arthropathy and 1 with severe arthropathy left ankle. Severe: n = 8 (6 = SHA; 2 = SHB) Moderate: n = 1 (HA) Prophylaxis: n = 9 (2-3/wk 'according to medical criteria') Randomized into 2 groups: A: Passive joint mobilizations (n = 4) B: Manual therapy (n = 5)	6 wk study period 2 h per week (both groups) Both groups: infrared lamp start of session Group A: passive joint mobilizations and muscle exercises and proprioception Group B: had manual therapy (joint distractions) and muscle exercises and proprioception Both groups cryotherapy to finish session
Cuesta-Barriuso 2014[24] (Spain)	Randomized control pilot study	31 adults with haemophilia (mean age 35.29) and ankle arthropathy (6 unilateral and 25 bilateral arthropathy) Severe (n = 19) Moderate (n = 12) Randomized into 3 groups: Manual Therapy: n = 11(HA = 8; HB = 3) (Severe = 9; Moderate = 2) - Prophylaxis: n = 8 - On-Demand: n = 3 Education: n = 10 (HA = 9; HB = 1) (Severe = 7; Moderate = 3) - Prophylaxis: n = 7 - On-Demand: n = 3 Control group: n = 10 (HA = 9; HB = 1) (Severe = 3; Moderate = 7) - Prophylaxis: n = 2 - On-Demand: n = 8	12 wk study period Manual Therapy group: 2× 60 min per session per week Thermotherapy, ankle joint traction, passive muscle stretching gastrocnemius, Isometric and resisted exercises, proprioception exercises, local cryotherapy Education and exercise group: (6× 90 min sessions once a fortnight). Theory: ankle anatomy/biomechanics, joint bleeding, synovitis, arthropathy, proprioception, pain and mobility Practical: Ankle ROM exercises, strengthening exercises, exercise for mobility and pain management, proprioception exercises. Encouraged to walk, cycle and swim. Group support and Q&A feedback throughout
Cuesta-Barriuso 2017[25] (Spain)	Randomized controlled trial	20 adults with haemophilia (mean age 30.95) with at least one joint affected by haemophilic arthropathy. Severe: n = 10 Moderate: n = 3 Mild: n = 7 (HA = 16; HB = 4) Prophylaxis: n = 7 On-Demand: n = 13 Randomized to 2 intervention arms: Control: n = 10 (HA = 9; HB = 1) (Severe = 2; Moderate = 3; Mild = 5) Prophylaxis: n = 2 On-Demand: n = 8 Education with home exercise programme (HEP): n = 10 (HA = 7; HB = 3) (Severe = 8; Mild = 2) Prophylaxis = 5 On-Demand = 5	15 wk study period Educational sessions every 2 wk for 60 min alongside home exercise programme: Control group advised to continue with the same daily professional and sporting routines that they had been following *Education/HEP:* Theory: anatomy/biomechanics elbow, knee and ankle joints, haematoma management, exercise theory, joint bleeds, synovitis and arthropathy, proprioception, physical activity and sport. Practical: muscle stretching for the upper and lower limbs, strengthening exercises for quadriceps, hamstrings, biceps/triceps and calves, proprioception exercises, encouraged to do 20 min walk per day

Outcomes	Notes	GRADE assessment
Pain intensity ankle: VAS HR QoL: A36 Hemophilia QoL questionnaire Ankle ROM: Dorsi-, plantar-flexion, inversion, eversion Proprioception: Romberg's test	Not stated what baseline was for participants in each group (ie how many ankles (uni-or bilateral)—were affected in each individual)	Low ⊕⊕OO
Calf Strength: Calf circumference Ankle ROM: Dorsi-, plantar-flexion, inversion, eversion Ankle pain: VAS	Authors note that there were differences between the groups in terms of radiological deterioration, ROM and pain perception. Potential variance between groups associated with severity of haemophilia. Control group had mostly moderate and on-demand treatment participants, whereas both intervention arms had mostly severe and on prophylaxis. Participants handed records of home exercise compliance in every 2 wk—but it was not stated if these were fully complete.	Very Low ⊕OOO
Orthopaedic joint assessment: Gilbert Score Pain intensity ankle, knee, elbow: VAS Quality of life: A36 questionnaire Illness behaviour questionnaire (IBQ)	This appears to be the same group of participants that have already been enrolled in all of the authors previous papers. (? bias of results if participants have been exposed to previous interventions)	Low ⊕⊕OO

(Continues)

TABLE 1 Continued

Trial and location	Methods	Participants	Intervention
Cuesta-Barriuso 2018[18] (Spain)	Single blind randomized study	27 men with haemophilia (mean age 34.48 yr) and elbow joint arthropathy Overall: Severe (n = 17) Mild (n = 10) (HA = 22; HB = 5) Prophylaxis: n = 15 On-Demand: n = 12 Randomized to 3 groups- Manual therapy: n = 9 (HA = 6; HB = 3) (Severe = 8, Mild = 1) Prophylaxis = 7 On-Demand = 2 Education: n = 9 (HA = 8: HB = 1) (Severe = 6; Mild = 3) Prophylaxis = 6 On-Demand = 3 Control: n = 9 (HA = 8; HB = 1) (Severe = 3; Mild = 6) Prophylaxis = 2 On-Demand = 7	12 wk study period Follow-up assessment 6 mo after end of intervention. Manual therapy group 2× 60 min per session per week: Thermotherapy, elbow joint traction, elbow muscle stretching, joint compression technique, passive muscle stretching biceps/triceps, PNF of upper limb, local cryotherapy. Education group (90 min session every 2 wk, plus home exercise programme 20-30 min daily): Theory: anatomy/biomechanics of elbow, haematoma management, joint bleed, synovitis, arthropathy, proprioception, physical activity and sport. Practical: Elbow ROM exercises, strengthening exercises, exercise for mobility and pain management, proprioception exercises Control Group: usual routine
Donoso-Ubeda 2018[29] (Spain)	Non randomized, controlled before and after trial	16 men with haemophilia (mean age 40.69) and haemophilic arthropathy of the knee and ankle. Severe (n = 12) Moderate (n = 4) Prophylaxis: n = 16 Mean freq. every 2.44 d (±0.51) Mean dose FVIII/FIX = 2625±619.13 units 2 groups: Fascial therapy (n = 8) Control (n = 8)	3 wk study period 3× 50-60 min session per week. Control: advised to maintain same level and conditions of physical work and activity. Intervention arm: Fascial therapy No description given of patient position. All manoeuvres done on both lower limbs except thoracolumbar technique. Superficial and deep fascial release techniques.
Eid 2015[26] (Saudi Arabia)	Randomized Trial	30 boys with haemophilia (aged 9-13), with a bleed frequency in their knees of at least once a week. Moderate Haemophilia A: n = 30 Prophylaxis: n = 30 (No regime stated) Randomized to 3 groups: Low level laser therapy (LLLT) (n = 15) Pulsed electromagnetic field therapy (PEMF) (n = 15)	12 wk study period Both Intervention 3 times per week. Both groups had a physiotherapy programme as well as the study intervention. LLLT: applied to 5 points including medial and lateral side patellar tendon, medial and lateral side knee adjacent to patella and over suprapatellar pouch. Applied for 40 s to each point. PEMF: solenoid adjusted to be over both knee joints. Parameters of treatment programme selected and adjusted as a frequency of 15 Hz, intensity of 20 gauss for 20 min. *Physical therapy program* In acute haemarthrosis: cold packs, isometric exercises. In subacute: isometric and isotonic exercises given additionally. Chronic arthropathy: hot packs, strengthening, proprioception and stretching exercises. All groups had a home programme

Outcomes	Notes	GRADE assessment
Safety of intervention Elbow ROM: Flexion/ extension Arm circumference Biceps strength Pain intensity elbow: VAS	Baseline imbalances between groups: more people with mild haemophilia in the control group (6) than the Manual therapy group (1). Median VAS at baseline in education and control group was 0. Results presented in median and IQR instead of mean and SD—emailed authors to request data in mean/SD which was made available	Low ⊕⊕OO
Joint health: Haemophilia joint health score 2.1 Hamstring flexibility: Finger to floor test Lumbar mobility: Schober test Pain intensity right and left knee and ankle in weight and non-weightbearing: VAS	No randomization	Very Low ⊕OOO
Pain intensity knee: VAS ROM knee Flexion/ Extension Swelling: Tape measure around knee Physical fitness: 6 min walk test (6MWT) Laboratory investigations: Erythrocyte sedimentation rate Complete blood count including white blood cells	Poor description of intervention especially the physiotherapy programme. It was unclear when the laser was delivered in the session. There are ethical concerns about why the investigators would expose both knees to PEMF as it did not state if both were affected (when the LASER group only treated one knee). Unclear if rate of haemarthrosis continued to be once per week throughout intervention period. No description of how acute, sub-acute haemarthrosis was assessed	Low ⊕⊕OO

(Continues)

TABLE 1 Continued

Trial and location	Methods	Participants	Intervention
El-Shamy 2016[28] (Saudi Arabia)	Single-blinded, placebo controlled randomized trial	30 boys with Haemophilia A (aged 9-13) with bilateral knee haemarthrosis. Severity of haemophilia not stated. Prophylaxis: n = 30 Regime not stated Randomized into 2 groups: Laser therapy (n = 15) Sham Laser group (n = 15)	3 mo study period. 3× 1 h sessions per week. Both groups: received a 'traditional' physiotherapy programme that included hot packs, muscle stretching and strengthening exercises, proprioceptive training, balance and gait training. Laser group: Laser from HIRO device. Positioning: knee flexed to 30 degrees. Initial phase performed with fast scanning for total of 400 J. Intermediate phase—applied hand piece to total 10 points (3 in medial knee, 2 in lateral knee and 3 above patella, and 2 below patella) with a fluency of 10 mJ/cm^2 and a time of 14 s at each point for a total of 150 J. Final phase—same as initial phase, except that slow manual scanning was used with a total energy of 200 J. Sham Laser group: HILT machine switched on with a visible light beam only—all parameters set up without switching the start position of the machine
Goto 2014[27] (Japan)	Prospective, controlled, randomized non blind comparative stud	32 men with haemophilia (mean age 41.8) with arthropathy in knees or ankles. Recruited across 4 sites Overall: Severe: n = 27; Moderate/mild: n = 5 HA = 26; HB = 6 Randomized into 2 groups: Home exercise programme with self-monitoring (n = 16) Severe = 13; Moderate/mild = 3 Prophylaxis = 14 On-Demand = 2 Home exercise alone (n = 16) Severe = 14; Moderate/mild = 2 Prophylaxis = 11 On-Demand = 5	8 wk study period. Both groups: given home exercise programme. Only difference is the participants in the intervention arm could review their progress on their monitors, whereas the control arm group could not. Home exercise programme—guidance about strengthening knee extensors, static stretching for knee flexors and standing balance training. Advice on promotion of physical activity given by physio to improve knee function. Knee extension strength training, static stretches and balance training Advice on leading an active life and doing non-contact sports were recommended for improving physical activity. ** physio recommended the exercise most appropriate to the physical condition of each patient to be done 10 times per day Self-monitoring: Participants were equipped with display activity monitors and feedback system via internet and mobile phone. When participants accessed the server to data input—feedback results appeared with time in form of graphs and tables. The number of times performed exercises, physical activity, bleeding frequency and injection of factor were recorded
Mazloum 2014[23] (Iran)	Quasi-experimental and prospective trial with a non-randomized pretest-post-test control group	40 people with haemophilia under 50 y old with impaired knee joint ROM. All severities—although exact numbers not stated. HA or HB—not stated Prophylaxis—not stated Randomized to 3 groups: Hydrotherapy (n = 14) Land-based exercise (n = 13) Control Group (n = 13) Clotting factor taken before participation in activity (dose not stated) (Average age in each study group = 33 y)	4 wk study period. Hydrotherapy: Warm up (5 min)—co-ordinated and rhythmic movement of lower limb in water. Exercises (30-45 min) for hamstrings stretching, quadriceps strengthening, from isometric to isotonic. Cool down (5 min) gentle stretching Land-based exercise: Warm up (5 min) simple stretching exercises for muscles surrounding knee. Main part (30-45) hamstrings stretching, quadriceps strengthening, progressing from isometric to isotonic. Cool down (5 min) of gentle stretching Control: Not stated what was advised

Note: GRADE Key: ⊕⊕⊕⊕—High Quality—Confident that true effect lies close to that of estimate effect; ⊕⊕⊕O—Moderate Quality—moderately confident in the effect estimate; ⊕⊕OO—Low Quality—confidence in effect estimate is limited; ⊕OOO—Very Low Quality—Very little confidence in the effect estimate.

Outcomes	Notes	GRADE assessment
Pain intensity knee: VAS Functional capacity: 6MWT Gait assessment: Stride length, step length, velocity and cadence—using GAITRite system		Very Low ⊕OOO
Self-efficacy for exercise questionnaire: Questionnaire not stated Exercise adherence questionnaire: Questionnaire type not stated Quadriceps strength: using hand held dynamometer ROM: Ankle—plantar-, dorsiflexion Knee—flexion/ extension Function: Modified functional reach test 10 m gait time Pain intensity: VAS Physical Activity levels— using activity monitor	Baseline imbalances of participants joint disease—ankle arthropathy was a much worse issue in the whole cohort even though the exercise plans carried out by participants was aimed at improving knee function. Unclear who delivered the programme to intervention group across the 4 sites and how the programme was delivered	Very Low ⊕OOO
Pain intensity knee: (VAS) Knee ROM: Flexion and extension	Number of sessions per week was not stated. 43 participants started study, but 3 dropped out (did not state from which group)	Very Low ⊕OOO

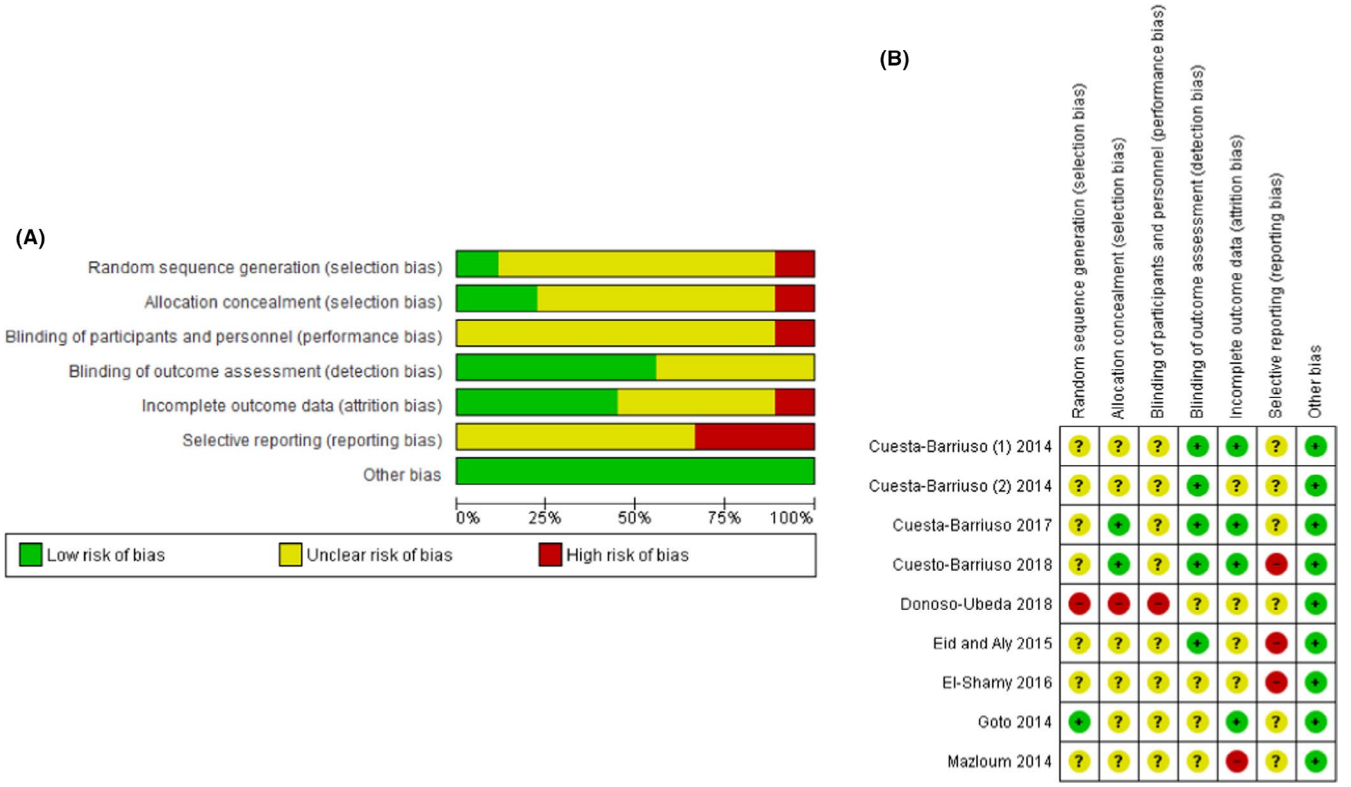

FIGURE 3 A, Risk of bias graph—author assessed risk of bias across all studies. (B) Risk of bias summary—author assessed risk of bias for each study [Colour figure can be viewed at wileyonlinelibrary.com]

4.1 | Primary outcomes

4.1.1 | Pain

All five trials included assessment of pain intensity using the visual analogue scale (VAS), with improvement in pain reported as a decrease in the VAS score. All were conducted on adults over 18 years of age, and apart from one study,[29] all were RCT's.

Elbow

There was no clear benefit on pain intensity when using manual therapies and education on elbow pain, MD −0.30 VAS (95% CI −0.92 to 0.32) or when using home exercises and education, MD −0.01 VAS (95% CI −0.34 to 0.36).

Knee

There was no clear benefit on pain intensity when using home exercises and education, MD −0.75 VAS (95% CI −2.13 to 0.63) or fascial therapy, MD −0.87 VAS (95% CI −2.81 to 1.07). Both hydrotherapy and land exercises were beneficial to knee pain intensity compared to no intervention. Hydrotherapy vs no intervention had a slightly stronger effect on pain intensity, MD −2.0 VAS (95% CI −3.28 to −0.72) compared to land-based exercise vs no intervention, MD −1.2 VAS (95% CI −2.54 to 0.14).

Ankle

There was no clear benefit on pain intensity with home exercises and education MD −0.55 VAS (95% CI −2.37 to 1.27), MD −0.3 VAS (95% CI −1.2 to 0.6), or with manual therapy and exercise MD 0.06 VAS (95% CI −1.47 to 1.6). Fascial therapy showed a small positive effect of the intervention on right ankle pain intensity, MD −0.76 VAS (95% CI −1.39 to −0.13), but this was a study with high risk of bias.

4.2 | Secondary outcomes

4.2.1 | Quality of life

Only one study[25] investigated the effects of patient education and home exercise programme (n = 10) compared to no intervention (n = 10) on patient reported quality of life. It is not clear if there is any beneficial effect of the intervention on quality of life, MD QoL 18.50 (95% CI −2.25 to 39.25).

4.2.2 | Function

None of the studies measured function as a outcome of intervention.

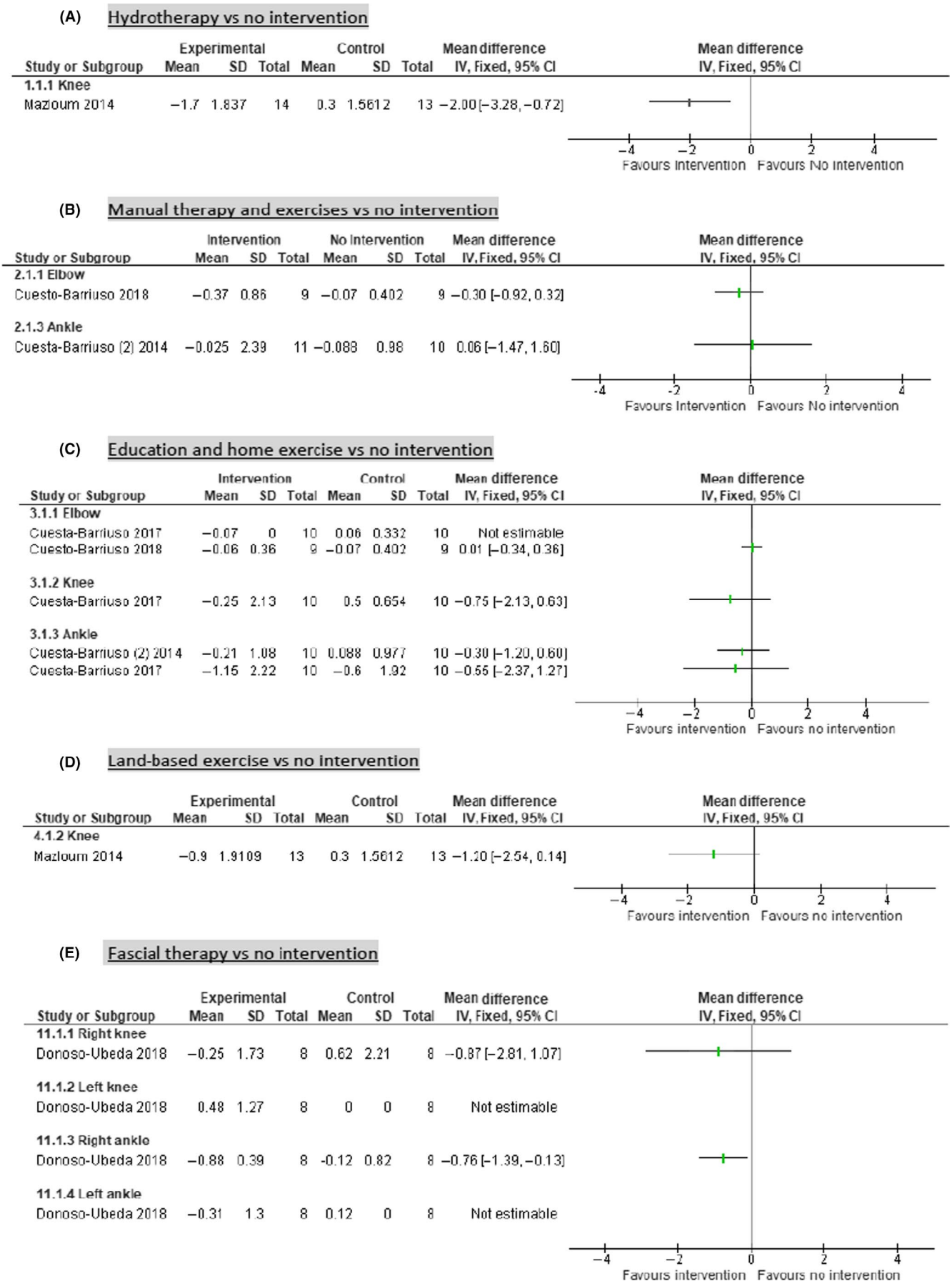

FIGURE 4 Comparison of physiotherapy intervention vs no intervention—Pain [Colour figure can be viewed at wileyonlinelibrary.com]

5 | PHYSIOTHERAPY INTERVENTION A VS PHYSIOTHERAPY INTERVENTION B

Seven studies were included in this comparison (Figure 5).[18,22-24,26-28]

5.1 | Primary outcomes

5.1.1 | Pain

All seven trials included assessment of pain intensity using the visual analogue scale (VAS), with improvement in pain reported as a decrease in the VAS score. Five were conducted on adults over 18 years of age, and two on children between the ages of 9 and 13.

Elbow

There was no clear demonstration of benefit for manual therapy and exercise over education and home exercises for elbow pain MD −0.31 VAS (95% CI −0.92 to 0.3).

Knee

Hydrotherapy has a more positive effect on knee pain than land-based exercise, MD −2.6 VAS (95% CI −4.02 to −1.18). LASER and exercise had a more positive effect on pain intensity than either sham laser left knee, MD −1.73 VAS (95% CI −2.23 to −1.23) right knee, MD −1.61 VAS (95% CI −2.09 to −1.13), or PEMF and exercise MD −1.07 VAS (95% CI −1.84 to −0.3).

Ankle

There was no clear benefit on pain intensity when comparing mobilization and exercise with manual therapy and exercise MD 0.4 VAS (95% CI −3.34 to 4.14), or manual therapy and exercise with home exercises and education MD 0.18 VAS (95% CI −1.38 to 1.75).

Pain (knee and ankle combined)

It is not clear if there any beneficial effect on knee and ankle pain of a self-monitoring home exercise programme compared to an exercise programme alone, MD 0.62 VAS (95% CI −0.37 to 1.61).

5.2 | Secondary outcomes

5.2.1 | Quality of Life

Only one study[22] investigated the effect of a joint mobilization and exercise intervention (n = 5) vs a manual therapy and exercise intervention (n = 4) on patient reported quality of life. The A-36 Haemophilia-QoL questionnaire was used. This is a 36 item questionnaire with a score range of 28-138 (higher score meaning better QoL). It is not clear if there is any beneficial effect on Quality of life from either intervention arm, MD −9.1 QoL (95% CI −47.2 to 29).

5.2.2 | Function

Three studies included a measure of function as an outcome measure of intervention.

It is not clear if there is any beneficial effect on function as measured by the 6MWT with LASER and sham LASER, MD 29.33 minutes (95% CI −9.48 to 68.14), or LASER and exercise compared to PEMF and exercise, MD 14.47 minutes (95% CI −21.34 to 50.38).

It is not clear if there is any beneficial effect with self-monitoring and exercise vs exercise alone on modified reach test, MD 0.1 cm (95% CI −7.64 to 7.84) or on 6MWT, MD 0.4 seconds (95% CI −0.84 to 1.64).

6 | DISCUSSION

This review presents the current evidence of trials utilizing a variety of physiotherapy approaches, with potential effect on pain intensity, quality of life and functional ability in PWH. It demonstrates that currently, there is low/very low quality of unclear evidence of effectiveness of many physiotherapy interventions on these outcomes.

The studies included in this review highlight the wide range of interventions being studied. They included joint manual therapy, passive joint mobilizations, exercise interventions, patient education, high intensity laser therapy (HILT), pulsed electromagnetic field treatment, hydrotherapy and fascial release therapy.

Pain is an issue that many PWH state is one of their major concerns,[30] yet no study included in this review defined pain as a specific inclusion criteria or ascertained if the presence of pain was of concern to participants. This may indicate assumptions made on the presence of pain based only on having haemophilia and/or arthropathy. Across many of the studies, the small differences in pre- and postintervention pain (VAS) highlight only a small change after intervention. It is unclear if this is due to a low pain VAS report preintervention (ie they had less/minimal pain upon starting the intervention) or a lack of effect of the intervention.

Only two studies included quality of life assessment,[22,25] and three included an assessment of function.[26-28] The minimal evaluation of psychological and social aspects of well-being alongside pain or basic joint function (such as ROM) makes no clear distinction of what the interventions mean to the individual taking part.

Physiotherapy trials can be considered a 'complex intervention'—that is, an intervention containing several interacting components. Dimensions of complexity can include the following: the number of and interactions between components in the same experimental and control interventions, the number and difficulty of behaviours required by those delivering or receiving the intervention, number of groups targeted by the intervention, the number and variability of outcomes being measured and the degree of flexibility or tailoring of the intervention permitted.[31] Haemophilia and its associated co-morbidities is a highly complex presentation, and as a result, any physiotherapy intervention would be, by-proxy, a complex intervention. Trials described here take no account of the potential complexity of the condition or the

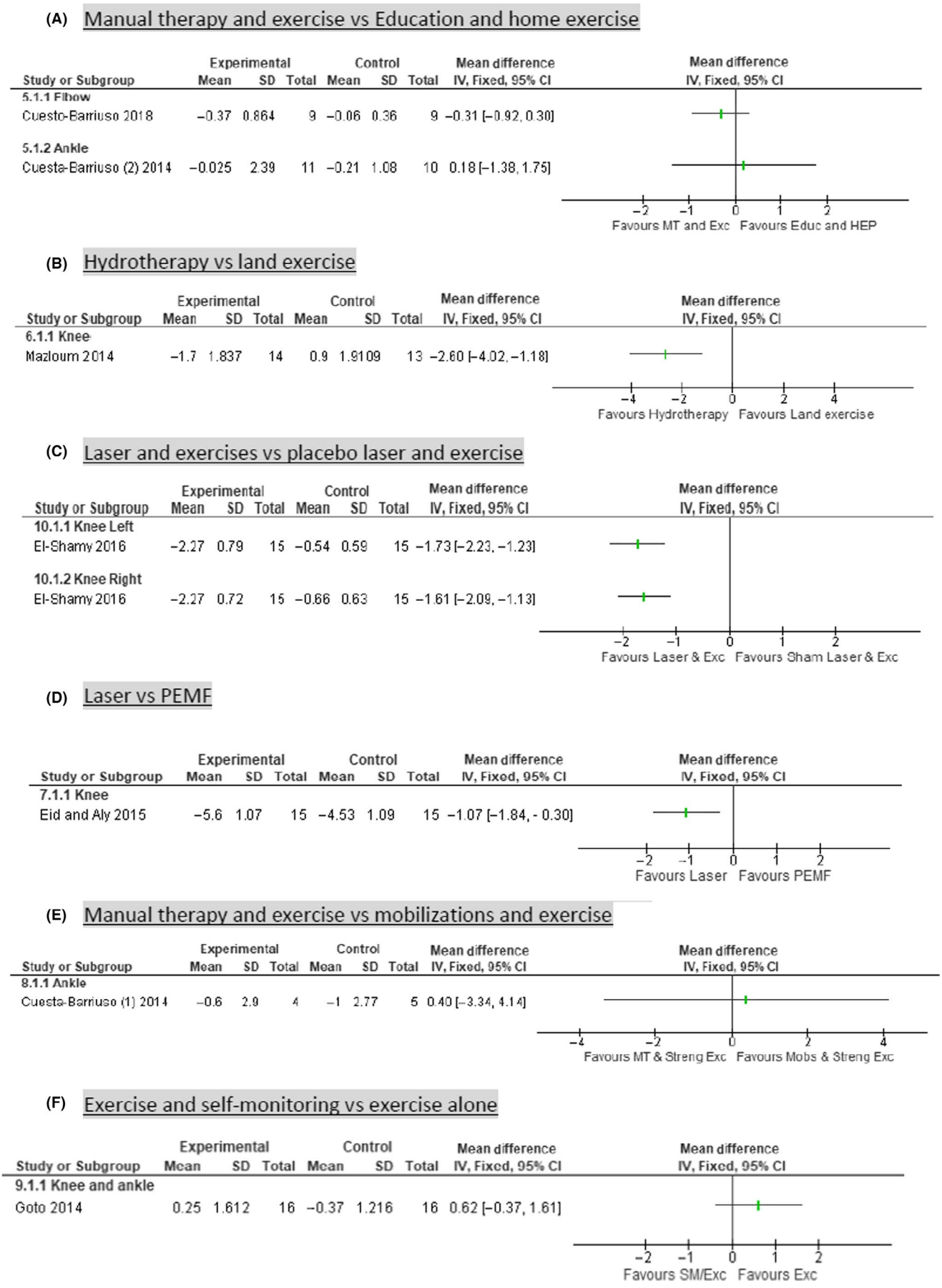

FIGURE 5 Comparison of physiotherapy intervention 'A' vs physiotherapy intervention 'B'—Pain [Colour figure can be viewed at wileyonlinelibrary.com]

intervention, thereby making it difficult to evaluate them in their practical effectiveness or to identify how they may be exerting their effects.

Education showed little positive effect when used in conjunction with exercise or manual therapy. It is not clear from the studies how the teaching curriculum was developed. Including health education without consideration for potential behaviour change models of action limits evaluation of how any education provision may be having its effect.[32]

Previous systematic reviews share some similarities to this review. However, the quality of some of those reviews, as well as their results and recommendations, differs to those presented here. Although described as a systematic review, an evaluation of exercise and sport in the treatment of PWH[33] lacked clear inclusion criteria as well as systematic analysis or comparison of data. In a narrative review of physical exercise, pain and musculoskeletal function in PWH Schäfer and colleagues[34] described the data for intervention effectiveness and concluded that exercise promoted a reduction in pain, improved ROM and strength in PWH. However, mean change from baseline together with confidence intervals was not reported or compared. They also reported low risk of bias in three studies that we assessed as having high risk,[22,23,27] although this may be due to different assessment tools being used.

A recent Cochrane Review on Exercise for haemophilia[35] was well conducted and included a broader range of outcomes in their analysis than this review. Similar to us, they noted major issues on study quality and stated that although exercise was likely safe, they urged caution with results as they stand.

Two further systematic reviews focussed on the treatment of chronic haemophilic ankle arthropathy[36] and physiotherapy in the treatment of haemophilic arthropathy.[37] The focus of the analysis in both was on the physiotherapy intervention itself rather than comparing the effects of those interventions on specific identified outcome measures. This makes it difficult to infer efficacy of any one specific intervention on measures such as pain and function. In contrast to our findings, the second review reported good study homogeneity, but it was not clear how this was evaluated.

Overall, the methodology and reporting quality of many of the included trials were poor. No study rated as high when being assessed for overall risk of bias. Many failed to provide details on randomization or participant allocation as well as appearing to omit some data in their overall results. High degree of trial heterogeneity was identified for both participants (severity of haemophilia, age range, location and number joints affected) as well as interventions (varied time frames for delivery, intervention components and outcome measures). Thus meta-analysis was not possible. Participant numbers were low for all included trials, and four of the trials were randomized pilot studies.[18,22,24,29]

Although overall safety from physiotherapy interventions was not included as an outcome for this review, it is acknowledged that physiotherapy interventions themselves may negatively influence pain, function and QoL. Safely participating in a rehabilitation programme is paramount from a haemostatic perspective as well as the perception of safety of the individual taking part. The limited detail on participant prophylaxis regimes limits further extrapolation of findings for others regarding intervention planning and safety, as does the heterogeneity of severity of disease in participants. None of the trials included only people with severe haemophilia—an important factor in considering the implications of potential effects of physiotherapy interventions, as severe haemophilia remains a diagnosis most likely to result in multi-joint arthropathy and pain. Further studies should seek to include all participant diagnostic and treatment information when reporting and publishing their results.

No studies appear to have involved PWH in the trial design, nor evaluated any qualitative measure of participation in such trials. As a rare disease, many PWH can be considered experts not just in their condition, but also in potentially identifying what matters to them in respect of rehabilitation interventions.

A strength of this review is the process of using two blinded reviewers throughout the process. Unlike many of the previous similar systematic reviews, we analysed the data to produce confidence intervals (CI's) and mean difference (MD) figures, allowing a good visual representation of effectiveness. A limitation is that we were unable to proceed to complete a meta-analysis of the data from any of the included studies. This precludes any clear recommendations for the use of physiotherapy interventions in the management of pain in haemophilia.

Better design of trials is required and should include PWH in the process. Specific and defined inclusion criteria relating to haemophilia disease severity, as well as pain as a self-reported symptom, are needed to better assess efficacy of any interventions.

The current use of only VAS in measuring pain intensity requires further scrutiny. Pain as a multi-modal, personal, lived experience is poorly evaluated when measuring intensity alone.[38] Further trials need to focus on how interventions may be designed to improve the physical, social, psychological and functional ramifications of a life-lived with pain.

7 | CONCLUSION

This systematic review highlights that there is currently an unclear demonstration of evidence for the use of physiotherapy interventions for pain management in people with haemophilia. LASER with exercise and hydrotherapy/land-based exercise appears to have some positive effect on knee pain in PWH. However, caution must be taken with this recommendation due to poor quality reporting and high risk of bias in both trials. It is not possible to make recommendations on any other physiotherapy intervention in the management of pain in haemophilia. Improved trial design and methodology will allow this emerging body of research to be effectively collated and compared, to further develop effective interventions for pain in haemophilia.

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CONFLICT OF INTERESTS

None of the authors have interests which may be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTION

PML, DS and MH contributed to the study design. PML and DS contributed to data extraction and analysis for the review. All authors contributed to the development and review of the manuscript.

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ORCID

Paul McLaughlin https://orcid.org/0000-0002-5962-7647
Pratima Chowdary https://orcid.org/0000-0002-6690-8586
Kate Khair https://orcid.org/0000-0003-2001-5958
David Stephensen https://orcid.org/0000-0002-6175-3343

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