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Title: The Effect of Hydrotherapy on Range of Motion and Pain in Hemophilia: A Meta-Analysis

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ABSTRACT

Purpose: The objective of this research was to assess how hydrotherapy influences range of motion (ROM) and pain among hemophilia patients.

Methods: This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines. A thorough literature search was carried out in October 2024, across several databases, including PubMed, ProQuest, ScienceDirect, and Cochrane. The Cochrane Risk of Bias (RoB) 2 tool and the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I V2) were applied for study quality assessment, while Review Manager (RevMan) 5.4 was utilized for meta-analysis.

Results: In total, three studies were analyzed, and the methodological appraisal showed that two had low risk and one had moderate risk of bias. Significant improvements in knee extension ROM (SMD = 1.17, 95% CI [0.15, 2.18], $p = 0.02$) and decreases in pain (SMD = -1.46, 95% CI [-2.00, -0.91], $p = < 0.0001$) were observed in the hydrotherapy group versus controls. However, knee flexion ROM improvement was not statistically significant (SMD = 2.17, 95% CI [-0.42, 4.77], $p = 0.10$).

Conclusion: Hydrotherapy demonstrates potential benefits in improving knee ROM and pain in hemophilia, particularly in knee extension. However, variability across studies limits the certainty of these findings. Further large-scale randomized controlled trials (RCT) with standardized intervention protocols are required to clarify long-term outcomes and encourage widespread clinical application.

Keywords: Hydrotherapy, Hemophilia, Rehabilitation, Range of motion, Pain

Highlights

- Hydrotherapy significantly improved joint range of motion in hemophilia
- Pain scores decreased after hydrotherapy compared with controls
- Evidence supports hydrotherapy as adjunct therapy in hemophilia care

Plain language

People with hemophilia, a rare inherited bleeding disorder, often develop problems in their joints. Repeated bleeding inside the joints can cause stiffness, pain, and reduced movement over time. These joint issues make daily activities difficult and can lower quality of life. Finding effective ways to improve movement and manage pain is very important for people living with hemophilia. One possible treatment is hydrotherapy, which means doing exercise in water. Water can support the body, reduce stress on the joints, and make movements easier and less painful. Because of these benefits, hydrotherapy has been used in people with other joint conditions, but its effects in hemophilia had not been clearly summarized.

In this study, we combined and analyzed results from several previous studies that tested hydrotherapy in people with hemophilia. We looked at how hydrotherapy affected two key outcomes: the ability of joints to move and pain. We found that hydrotherapy helped improved how much people could move their joints and reduce pain. These results suggest that hydrotherapy can be a useful addition to standard care for people with hemophilia.

Pain and stiff joints are not only medical problems, but they also affect independence, social participation, and overall well-being. Hydrotherapy offers a simple, non-invasive, and enjoyable option that can be included in rehabilitation programs. For patients, families, and healthcare providers, this means there is an accessible therapy that may improve comfort and quality of life for people with hemophilia.

Introduction

Hemophilia refers to an inherited disorder that occurs when plasma clotting factors are lacking or insufficient, leading to spontaneous bleeding in the joints, brain, skin, gums, or other tissue (1). It results from mutations on the X chromosome (2). The Annual Global Survey 2024 from World Federation of Hemophilia reported that 489,356 people were diagnosed with bleeding disorder, and 289,304 among them were attributed to hemophilia (3). While prophylaxis remains gold standard for managing hemophilia, curative treatments have not yet been found. Other treatments may improve quality of life, reduce morbidity and mortality, and prevent complications (4).

Exercise training and rehabilitation are applied as a non-pharmacological approach to numerous diseases (5). However, land-based exercises may increase joint loading and provoke pain or fear of movement, particularly in individuals with established arthropathy. This can limit exercise tolerance and participation in rehabilitation programs (6). Hydrotherapy makes use of water for therapeutic exercise, temperature control, the buoyant effect, and hydrostatic pressure to support mobility while lessening stress on the joints. It may promote muscle strength, improve joint mobility, and lower intra-articular pressure, pain, and swelling (7,8).

Hydrotherapy may prevent acute bleeding and chronic hemophilic arthropathy in patients with hemophilia by reducing joint weight bearing stresses and gravitational load during the functional exercise (8,9). Studies have reported that hydrotherapy increases overall physical improvement and reduces the number of joint bleeds (10,11). Despite existing studies, comprehensive meta-analyses examining its effectiveness in this group are lacking. Additionally, existing evidence remains inconsistent regarding the magnitude of its effects across studies. Differences in study design, intervention duration, and patient characteristics may contribute to the variability in reported outcomes. We hypothesized that hydrotherapy would be associated with improvements in joint mobility and pain reduction compared with land-based exercise interventions.

Material and methods

This review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines(12). Details of the protocol are available in International Prospective Register of Systematic Reviews (PROSPERO) with the following registration number: CRD42024594679.

Eligibility criteria

Type of studies

We included published studies and also attempted to identify unpublished or ongoing trials through clinical trial registries that investigated the effects of hydrotherapy improving joint ROM and pain on individuals with hemophilia. Hydrotherapy was defined as a structured, exercise-based program performed in a therapeutic pool, supervised by qualified personnel. The exclusion criteria comprised review articles, cross-sectional designs, case reports/series, conference proceedings, book chapters, opinion pieces, and animal studies.

Participants

This review included studies involving patients with hemophilia any type, age, or severity. Studies that did not focus on patients with hemophilia or included participants outside this population were excluded.

Variable of interest

This research was designed to assess the benefits of aquatic-based exercise or hydrotherapy on joint ROM and pain severity in patients with hemophilia of all types and severities.

Outcome of interest

The primary outcomes of interest in this study include improvements in joint ROM and pain, which are critical indicators of physical functionality in patients with hemophilia.

Search strategy and study selection

The database search was initially conducted on October 2024, and updated on November 2025, using several electronic databases including PubMed, ProQuest, ScienceDirect, Cochrane, PEDro, Clinicaltrials.gov, and WHO International Clinical Trials Registry Platform (ICTRP). Three independent reviewers performed the search using a combination of MeSH and keywords related to hemophilia, hydrotherapy, aquatic exercise, range of motion, and pain. The PubMed search strategy included the following Boolean structure: ("Aquatic therapy"[Mesh] OR "Hydrotherapy"[Mesh] OR "Aquatic therapy"[Text Word] OR "Hydrotherapy"[Text Word] OR "Water-based exercise"[Text Word] OR "Aquatic exercise"[Text Word] OR "Water therapy"[Text Word] OR "Pool exercise"[Text Word]). Search strategies for ProQuest, ScienceDirect, Cochrane, and PEDro were adapted using equivalent keyword and indexing terms, while ClinicalTrials.gov and WHO ICTRP were searched using the terms hemophilia, hydrotherapy, aquatic therapy, and exercise to identify ongoing or unpublished trials. Zotero software was employed to manage all studies gathered from the search, checked for duplication, and titles/abstracts screening was carried out independently by three reviewers, with concordance discussed after each round. Studies considered suitable were subsequently subjected to full-text evaluation based on the established inclusion and exclusion criteria. No publication year restriction was applied, and only human studies were included.

Data collection process

Information retrieved from each study included authorship, year, country, design, participant age and population, selection criteria, intervention applied, and outcomes assessed.

Summary measures

Joint ROM and pain severity after intervention were the main outcome. To represent the effect size, the Standardized Mean Differences (SMDs) with 95% confidence interval (95% CI) were extracted. P-values were also reported to indicate statistical significance.

Assessment of risk of bias/Quality assessment

The risk of bias for randomized controlled trials was assessed using the ROB 2.0 tool, which evaluates seven key aspects related to study validity, including the randomization process, allocation concealment, blinding of participants and outcome assessors, completeness of outcome data, selective outcome reporting, and other potential sources of bias. For non-randomized studies, the ROBINS-I V2 tool was employed, assessing potential bias arising from confounding factors, intervention classification, participant selection, deviations from intended interventions, missing data, outcome measurement, and the selection of reported results (13,14).

Each study domain was assessed for potential bias, which was classified into low, moderate, high, and critical categories. On the basis of these ratings, the overall quality of trials was assigned to one of four groups: (1) low risk of bias, (2) moderate risk of bias, and (3) high risk of bias, and (4) critical risk of bias.(13,14) All studies were appraised independently by three reviewers. Conflicting assessments were settled by discussion with the full review team until mutual agreement was established.

Publication bias was assessed quantitatively using Egger's regression test and visually through a funnel plot when ≥ 10 studies were available for a given outcome. A p-value of < 0.05 in Egger's test was considered indicative of potential publication bias.

Synthesis of results and statistical analysis

Data were extracted and synthesized using Review Manager (RevMan). Participants were classified into intervention (hydrotherapy) and control groups. Due to variations in outcome evaluation methods across studies, a random-effects model was applied, assuming heterogeneity in treatment effects and assigning more balanced weights to each study. This approach also allowed extrapolation to a broader population, particularly when additional studies were incorporated. Pooled effect estimates for continuous data were calculated using the inverse variance method. For proportional outcomes, if applicable, the Mantel-Haenszel method was used to calculate pooled effect estimates based on categorical data. Since different measurement scales were used across studies, SMDs were selected as the most appropriate effect size for continuous outcomes. This approach allows for the comparison of results across studies that used different instruments or units to assess the same outcome. Heterogeneity was assessed using the I^2 statistic. Results were considered statistically significant when the p-value was below 0.05.

Confidence in cumulative evidence

Confidence in the body of evidence was evaluated according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) framework (15). Under the GRADE system, evidence quality is judged based on risk of bias, relevance to the research question, consistency across studies, precision of estimates, and potential publication bias. Evidence quality was classified into four categories: high, moderate, low, and very low.

Result

Figure 1 provides a detailed overview of the study selection process and its outcomes. The database search yielded 477 records. After removing 46 duplicates, 431 were screened, with 417 excluded. Of 14 full-texts sought, one was unretrievable, and 10 were excluded. Altogether, three studies were deemed eligible for inclusion in the present systematic review and meta-analysis (16–18) with publication years ranging from 2013 and 2015.

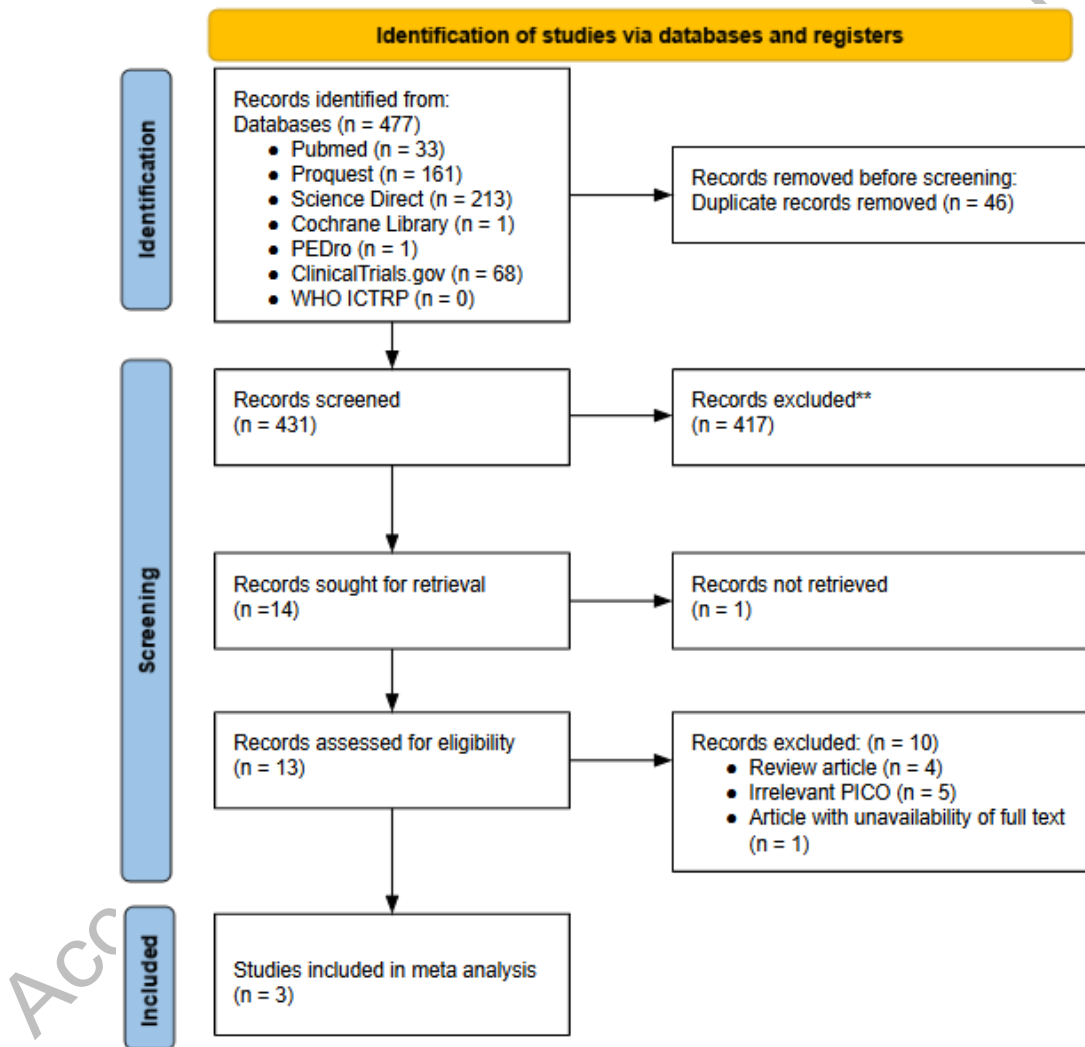


Figure 1

Quality assessment

The ROBINS-I framework was employed to evaluate the risk of bias in the included studies, as illustrated in Figure 2. Two studies conducted (Mazloun *et al.* and Kargarfard *et al.*) had a low risk of bias, while one study (Azab *et al.*) showed a moderate risk (16–18).

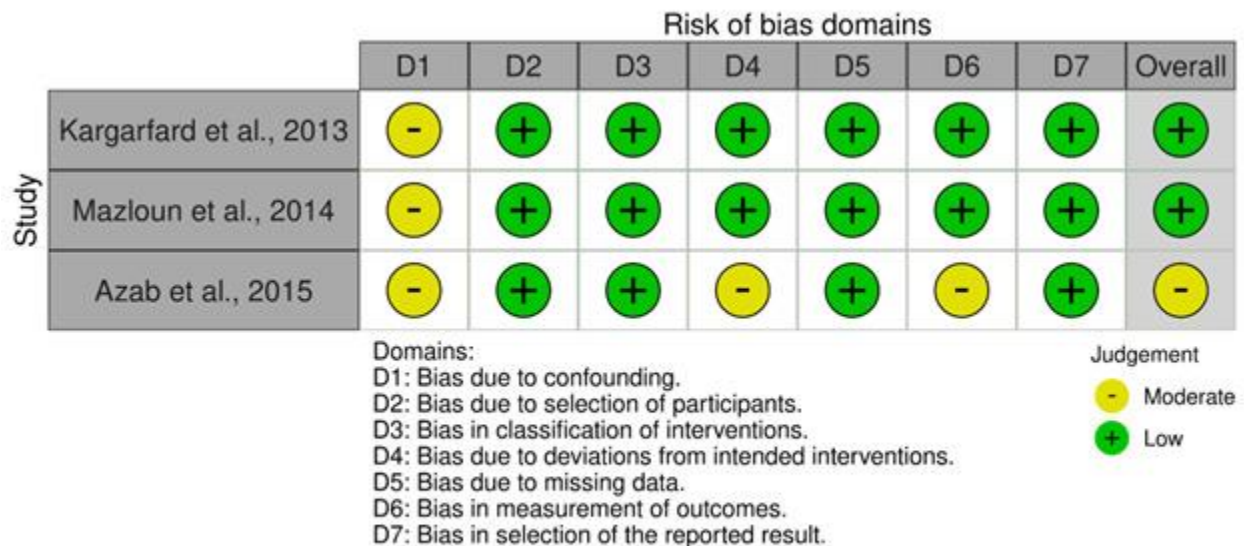


Figure 2

Characteristics of the included studies

Across the three quasi-experimental trials, a total of 44 participants were allocated to hydrotherapy interventions, while 43 were assigned to control groups. Details of the included studies, including sample size, age, hydrotherapy protocol, and measured outcomes, were compiled and are displayed in Table 1. Participants' mean ages varied between 22.9 and 33.4 years in the hydrotherapy group and between 18.1 and 33.6 years in the control group. Two studies were conducted in Iran (16,18) and one in Egypt (17). The hydrotherapy protocols varied across studies.

Table 1. Study Characteristics

Author, publication year, country	Type of study	Population				Hydrotherap y protocol	Outcome of interest
		Total population (n)		Age (years)			
		Hydrotherap y	Contro l	Hydrotherap y	Control		
Kargarfard , 2013, Iran (16)	Quasi experiment al	10	10	22.90±7.60	18.10±6.2 6	Warm up: Progressive aerobic activity. Main plan: Ten water- based movements— five for the upper limbs and five for the lower limbs— performed for one minute each with maximum effort or within a tolerable pain range. Cool down: Flexibility exercises to enhance joint ROM, tailored to the extent of muscle and joint damage, and lasts for five minutes.	Significant difference of knee flexion and knee extension between both groups after interventio n.
Mazloun, 2014, Iran (18)	Quasi experiment al	14	13	33.4±10.5	33.6±9.2	Warm up: 5 minutes of coordinated and rhythmic movement of	Significant difference of pain score, knee flexion and

						the lower limb in water. Main part: 30-45 minutes of hamstring stretching, quadriceps strengthening: First isometric with progress to isotonic. Cool down: 5 minutes of gentle stretching.	knee extension between both groups after intervention.
Azab, 2015, Egypt (17)	Quasi experimental	20	20	10.62±1.123	10.56±1.11	ROM exercise: repeated knee flexion and extension in sitting, lying back and lying on stomach position. Strengthening exercise: repeated isometric hold of thigh muscles while lying back, knee extension on sitting position and partial squats.-	Significant difference of pain score, knee flexion and knee extension between both groups after intervention.

ROM, range of motion.

Final results

All included studies reported statistically significant differences in knee extension outcomes between participants receiving hydrotherapy and those in control groups (16–18). (Table 2B), however only two studies showed significant differences in knee flexion (17,18) (Table 2A). Both studies assessing pain showed significant differences between the groups (17,18) (Table 2C). GRADE assessment is shown in Table 3.

Table 2A. Knee Flexion

Author, publication year, country	Knee Flexion ROM (mean \pm SD)		
	Hydrotherapy	Control	P
Kargarfard, 2013, Iran (16)	140.5 \pm 6.43	138.30 \pm 3.60	0.741
Mazloun, 2014, Iran (18)	118.50 \pm 13.4	105.5 \pm 22.2	<0.001
Azab, 2015, Egypt (17)	123 \pm 1.4	115.1 \pm 1.34	<0.05

ROM, range of motion; SD, standard deviation.

Table 2B. Knee Extension

Author, publication year, country	Knee Extension ROM (mean \pm SD)		
	Hydrotherapy	Control	P
Kargarfard, 2013, Iran (16)	-4 \pm 9.26	-6.50 \pm 6.69	0.001
Mazloun, 2014, Iran (18)	-7.1 \pm 4.9	-12.1 \pm 4.1	<0.001
Azab, 2015, Egypt (17)	-8.7 \pm 1.01	-11.3 \pm 1.4	<0.05

ROM, range of motion; SD, standard deviation.

Table 2C. Pain

Author, publication year, country	VAS (mean \pm SD)		
	Hydrotherapy	Control	P
Mazloun, 2014, Iran (18)	5.2 \pm 1.3	6.8 \pm 1.0	<0.001
Azab, 2015, Egypt (17)	2.8 \pm 1.32	5.69 \pm 2.23	<0.05

VAS, visual analog scale; SD, standard deviation

Table 3. GRADE evidence profile.

Outcome	Number of Studies	Quality Assessment						Summary Findings	
		ROBIN S-I	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall quality of evidence	MD total	95% CI (upper, lower)
Knee Flexion	3	No serious	Serious ^a	No serious	Serious ^b	No serious	Low	2.15	-0.46, 4.77
Knee Extension	3	No serious	Serious ^a	No Serious	No serious	No serious	Moderate	1.09	0.22, 1.97
Pain	2	No serious	Serious ^a	No Serious	No serious	No serious	Moderate	-2.09	-3.61, -0.58

^aI² results >75% are considered as high heterogeneity; ^bCI crosses cross the null; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ROBINS-I, Risk of Bias In Non-randomized Studies - of Interventions; MD, Mean difference; CI, Confidence Interval.

Meta-analysis results

The pooled results for each outcome are displayed in Figure 3 (A–C) and are reported as SMD with 95% confidence intervals. In Panel A, The SMD indicates that hydrotherapy produced a non-significant overall effect on knee flexion compared to the control group. (SMD = 2.17, 95% CI [-0.42, 4.77], $p = 0.10$). The most significant improvement is observed in Azab et al. (17) with an SMD of 5.65 (95% CI [4.21, 7.09]), while Kargarfard et al. (16) shows the least improvement (SMD = 0.40, 95% CI [-0.48, 1.29]). The high heterogeneity ($I^2 = 95\%$) suggests variation in the effects across studies. Panel B demonstrates a statistically significant improvement on knee extension with hydrotherapy compared to controls (SMD = 1.17, 95% CI [0.15, 2.18], $p = 0.02$). Among the studies, Azab et al. (17) presents the most substantial effect (SMD = 2.09, 95% CI

[1.30, 2.87]), while Kargarfard et al. (16) shows a smaller effect (SMD = 0.30, 95% CI [-0.59, 1.18]). High heterogeneity is noted ($I^2 = 78\%$). Panel C illustrates the SMD for pain outcomes, showing a significant reduction favoring hydrotherapy over the control group, as VAS scores were higher in the control group (SMD = -1.46, 95% CI [-2.00, -0.91], $p = < 0.0001$). The greatest reduction is observed in Azab et al. (17) with an SMD of -1.55 (95% CI [-2.26, -0.83]), followed by Mazloun et al. (18) with an SMD of -1.33 (95% CI [-2.18, -0.48]). Low heterogeneity is observed ($I^2 = 0\%$). Considerable heterogeneity was observed across outcomes, this variability may be associated with differences in participant age ranges, baseline joint status, and variation in hydrotherapy protocols (e.g., duration, frequency, and therapeutic focus). These factors likely contributed to the diverse effect sizes observed across studies. Because fewer than 10 studies were available for each outcome, funnel plots were not generated. This limitation reduces the ability to visually assess publication bias.

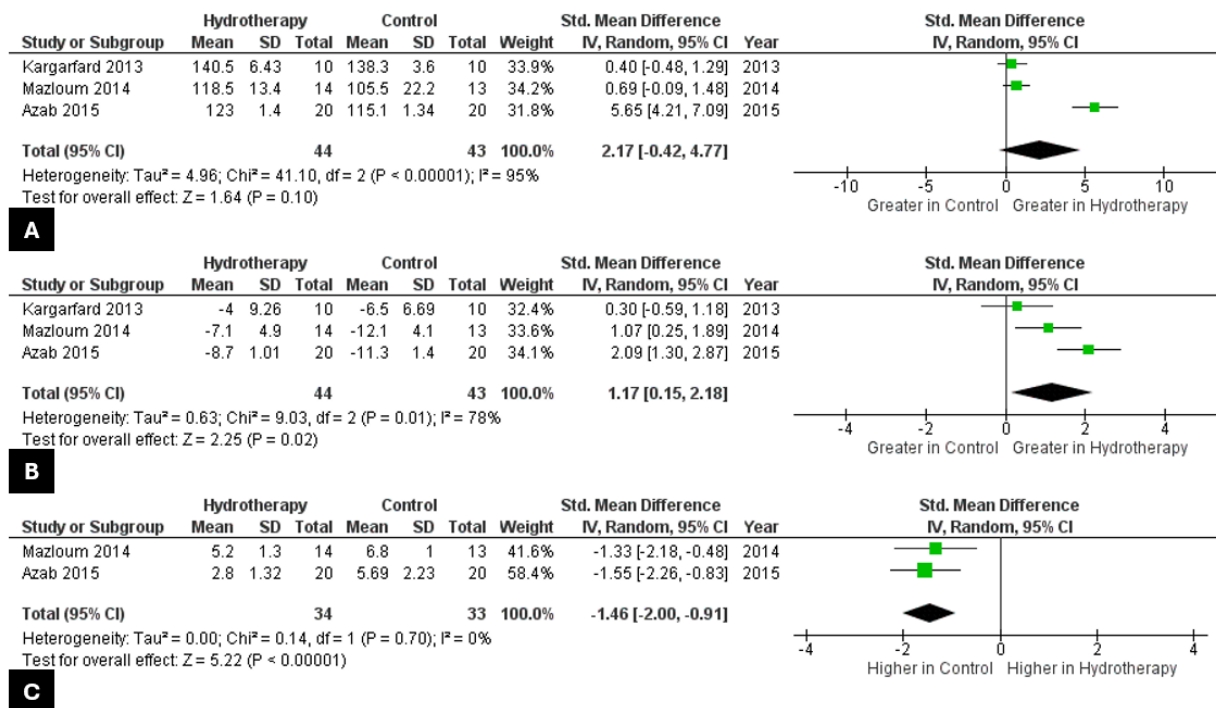


Figure 3

Discussion

Hemophilia is an X-linked condition characterized by a partial or total deficiency of clotting factor VIII and factor IX, leading to recurrent joint bleeding and progressive hemophilic arthropathy, marked by chronic inflammation, cartilage destruction, and joint deformities, resulting in significant physical impairment. The resulting limitations in mobility and daily activities negatively impact the overall functionality and quality of life (19,20). Common complications include muscle atrophy, restricted joint mobility, reduced functional capacity, and the presence of sarcopenia (21).

Hydrotherapy a controlled, low-impact environment where buoyancy reduces joint load and hydrostatic pressure supports circulation, pain reduction, and muscle relaxation. These properties allow patients with hemophilia to exercise with lower risk of trauma-induced bleeding while still engaging in strengthening, mobility, and functional training (22,23). The knee is one of the most frequently affected joints since it is subjected to substantial mechanical stress and weight-bearing forces, as well as being highly vascularized (24–26)

In this meta-analysis, hydrotherapy demonstrated a beneficial effect on knee outcomes. Although the improvement in knee flexion ROM (SMD 2.17; $p = 0.10$) did not reach statistical significance, the pooled estimate showed a trend toward ROM improvement. In clinical practice, this magnitude typically corresponds to an improvement large enough to translate into better ability to bend the knee during daily activities such as squatting, stair descent, and floor-to-standing transitions. The lack of statistical significance is likely influenced by small sample sizes and between-study variability, rather than the absence of a real therapeutic effect (27). Importantly, a targeted update of the literature search did not identify any recently published randomized trials reporting knee

flexion outcomes that would materially alter the pooled estimate. Knee extension showed a statistically significant improvement (SMD 1.17; $p = 0.02$), suggesting a clinically relevant benefit of hydrotherapy. Improvements in terminal knee extension have substantial functional impact—reducing quadriceps fatigue, improving gait symmetry, and alleviating joint loading during stance phase. For patients with hemophilic arthropathy, where flexion contractures are common and strongly associated with pain and long-term disability, restoring knee extension directly supports better mobility and reduces the risk of progressive joint degeneration (25). Nevertheless, the moderate heterogeneity observed suggests that the magnitude of benefit may vary across patient populations and intervention protocols. Therefore, while the direction of effect supports a beneficial role of hydrotherapy, the clinical impact should be interpreted with appropriate caution.

For pain, hydrotherapy produced a large effect size (SMD -1.46 ; $p < 0.0001$). A reduction in pain suggests that patients are likely experiencing less discomfort during daily activities such as walking, squatting, or navigating stairs (28). Decreased pain may also lower reliance on analgesics, reduce fear-avoidant behavior, and improve participation in rehabilitation, ultimately supporting better functional outcomes. In practice, even a moderate improvement in pain can create a positive feedback loop in which patients move more confidently, maintain healthier joint mechanics, and prevent further decline (29). Although the pooled effect suggests a robust analgesic benefit, the presence of heterogeneity indicates that pain reduction may differ depending on factors such as intervention intensity, disease severity, and baseline joint status. Consequently, these findings support the clinical relevance of hydrotherapy for pain management while underscoring the need for individualized application and further standardized trials.

Participant age and hemophilia severity varied across the included studies. Azab et al.(17) focused on children aged 10–13 years, while the other 2 studies (16,18) included adults. The direct effect

of age on hydrotherapy outcomes for knee ROM and pain was not examined in any study, limiting the ability to assess differential responses between younger and older patients. Severity of hemophilia among the studies also varied, ranging from mild to severe, which may influenced the outcome. Hydrotherapy protocol difference also contributed to heterogeneity, ranging from purely aquatic exercises (17), to progressive strength training in water (18), and high-intensity aquatic movements adjusted for pain tolerance (16). Despite these differences, all interventions shared key elements such as warm-up exercises, ROM training, and muscle strengthening movements.

GRADE assessment rated low for knee flexion ROM due to inconsistency and imprecision, while knee extension ROM and pain outcomes received a moderate quality due to inconsistency. The small number of available trials (≤ 3 per outcome) also limited subgroup and sensitivity analyses, making it difficult to determine whether factors such as age or chronicity of joint disease modify treatment response.

The meta-analysis revealed high heterogeneity in knee flexion ROM ($I^2 = 95\%$) and pain ($I^2 = 83\%$), with moderate heterogeneity in knee extension ROM ($I^2 = 71\%$). While such variability indicates differences in effect sizes across studies, it does not undermine the reliability of statistically significant results. However, cautious interpretation is required, as these differences may reflect real clinical variation rather than random error. Contributing factors include diverse hydrotherapy protocols, varying in duration, intensity, and focus, such as stretching, proprioceptive, strength, or aerobic training, which likely influenced outcomes. Study populations also differed in hemophilia severity. Some included a full spectrum of cases, while others focused on a single severity level. Since joint damage and baseline mobility vary by severity, this likely impacted responsiveness to therapy. Pre-existing joint limitations may have reduced improvements

in more severely affected individuals. Age may have played a minor role, as children's greater flexibility and activity levels could affect treatment response.

To the best of our knowledge, this study represents the first meta-analysis systematically examining the effects of hydrotherapy on ROM and pain in hemophilia. While a systematic review on this topic was published in 2019, it included only one study assessing ROM, making our meta-analysis the first comprehensive synthesis of multiple studies on this subject (9). All studies used goniometry to assess ROM, with one study (17) utilizing an electro-goniometer, while the other studies employed a standard universal goniometer (16,18). Pain was consistently evaluated using the VAS across all studies. These standardized measurement tools enhance the comparability of findings. Despite its strengths, our meta-analysis has certain limitations. Key aspects of hemophilia-related joint health, such as joint bleeding frequency and long-term joint integrity, were not assessed in the included studies. Additionally, while our study encompassed a broad spectrum of hemophilia severity, we were unable to conduct subgroup analyses based on age or baseline joint function due to limited data. The limited number of studies included also restricted our capacity to determine whether hydrotherapy's effectiveness differs according to the chronicity of joint damage.

Conclusion

Hydrotherapy appears to offer beneficial effects on knee ROM and pain reduction in patients with hemophilia, supporting its role as a rehabilitation intervention. While knee extension ROM showed a statistically significant improvement, knee flexion ROM did not reach significance, possibly due to variability in study protocols and participant characteristics. The presence of heterogeneity across studies indicate that the strength of these conclusions should be interpreted with some caution. Variability in participant characteristics, disease severity, and differences in hydrotherapy protocols across studies may have contributed to inconsistent effect sizes, which reduces the overall certainty of the pooled estimates. Since the knee is one of the most commonly affected joints in hemophilia due to recurrent hemarthrosis, these findings suggest that hydrotherapy may play a role in supporting joint function and symptom management. Future research should focus on its long-term impact on joint health, standardized hydrotherapy protocols, and more homogeneous patient populations are necessary to ensure reproducibility and clarify the degree of benefit that hydrotherapy can reliably offer.

Future directions

We propose that hydrotherapy could serve as a primary rehabilitation approach rather than just an adjunct to conventional therapy based on our findings. However, the lack of a standardized hydrotherapy protocol suggests the need for a structured rehabilitation guideline. A standardized approach would help ensure consistency in treatment and optimize therapeutic outcomes. Further investigations should examine the prolonged benefits of hydrotherapy, particularly concerning joint bleeding rates and protection against joint deterioration.

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Author contributions

Conceptualization, KAC, APA, JN, MA; Methodology, KAC, APA, JN, MA; Investigation, KAC, APA, JN, MA; Writing – Original Draft, KAC; Writing – Review & Editing, KAC, APA, JN, MA; Funding Acquisition, none; Resources, all authors; Supervision, all authors.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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