A preliminary case series evaluating the safety and immediate to short-term clinical benefits of joint mobilization in hemophilic arthritis of the lower limb

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ABSTRACT

Objectives: Arthritis resulting from recurrent intra-articular bleeding in individuals with hemophilia can be severely debilitating due to joint pain and stiffness with subsequent loss of mobility and function. Very limited studies have investigated the potential benefits of joint mobilization for this condition. This case series is a preliminary investigation of safety, as well as immediate and short-term clinical benefits, associated with gentle knee and ankle joint mobilization in people with hemophilic arthropathy.

Methods: A single intervention of joint mobilization was applied to the affected knees and/or ankles of 16 individuals with severe or moderate hemophilia within a public hospital setting. Adverse events, as well as immediate (pain-free passive joint range, Timed Up and Go Test with maximum pain numerical rating scale) and short-term (Lower Extremity Functional Scale) effects of the intervention were evaluated with a repeated measures ANOVA.

Results: There were no adverse events. An immediate significant increase was observed in pain-free passive ankle joint range of motion ($p < 0.05$) following the joint mobilization intervention.

Discussion: The findings of this case series suggest that gentle joint mobilization techniques may be safely considered as part of a multimodal management approach for hemophilic arthropathy.

KEYWORDS

Joint mobilization; manual therapy; hemophilia; arthritis; rehabilitation

Introduction

Hemophilic arthropathy is a common problem in patients with hemophilia caused by recurrent intra-articular bleeding (hemarthrosis), sometimes in the absence of any identifiable trauma. This can be a severe and disabling form of arthritis,^[1] with ankles and knees the most commonly affected joints in the lower limbs.^[2] Hemophilic arthropathy may include cartilage erosion, synovitis, contractures, and gross bony changes.^[3] Patients present clinically with significant pain, difficulty with mobility, and an increased risk of falling.^[4] There may also be devastating effects on capacity for self-care, work, and leisure activities, adversely impacting on quality of life.^[5,6]

Recommended management strategies for patients with hemophilic arthropathy include physiotherapy interventions such as exercise.^[7–11] From a physiotherapy perspective, a usual goal of management in these patients is to improve pain-free joint range. Therefore, manual therapy techniques (techniques applied with the therapist's hands such as gentle joint mobilization) can be a potential treatment option. These techniques use low velocity oscillating pressure to induce

motion of articular surfaces to facilitate improvements in joint mobility and pain. Mechanistic studies in non-hemophilic populations have shown joint mobilization techniques to induce immediate neurophysiological effects in individuals with painful musculoskeletal conditions, including pain modulation, reduced muscle hypertonicity, and improvements in kinesiophobia.^[12–14] In accordance, there is clinical trial evidence for the immediate^[15] and mid-term^[16,17] benefits of joint mobilization techniques for osteoarthritis of the knees as a stand-alone treatment. Systematic review evidence also suggests that the benefits of exercise in alleviating the pain associated with knee osteoarthritis is superior when combined with joint mobilization (effect size 0.69) compared to exercise alone (0.34–0.38).^[18] However, despite the evidence for joint mobilization in knee osteoarthritis, there is a paucity of studies investigating this intervention in hemophilic arthropathy.

Studies showing beneficial effects of joint mobilization in hemophilic arthropathy have been limited to its inclusion within multimodal management, combining joint mobilization with other interventions such as exercise, splinting, and gait retraining.^[19,20] A randomized

controlled trial showed improved outcomes in pain scores and calf muscle circumference in patients who received 12 weeks of multimodal physiotherapy (including joint mobilization, hot and cold packs, and supervised exercise) compared to an education plus home exercise group, and a control group.[21] However, it is still questionable if joint mobilization would provide measurable clinical benefits to this patient group as a stand-alone intervention. Additionally and foremost, the safety of applying joint mobilization techniques in this patient group who can experience hemarthrosis without apparent trauma warrants further evidence.

The aim of this case series was to investigate the immediate and short-term effects of a single session of joint mobilization in patients with hemophilic arthropathy from both a safety and clinical benefit perspective. It was intended as a preliminary investigation to provide feasibility data to underpin future larger scale studies investigating the specific effects of manual therapy in this challenging health condition.

Methods

Participants

Sixteen individuals (average age of 45 years) participated and included 14 volunteers with severe, and two with moderate, hemophilia. Four subjects were on prophylactic factor replacement. Potential participants were identified as those under the care of the Queensland Hemophilia Centre at the Royal Brisbane and Women's Hospital. Public Health Act approval was acquired to access the Australian Bleeding Disorder Registry electronic database to identify potential subjects.

Participants were included if aged between 18 and 70 years with moderate to severe Hemophilia and a diagnosis of hemophilic arthropathy of the knee and/or ankle. Diagnosis was provided by the Specialist Haematologist (J.R.) made on the basis of clinical history and physical assessment findings and confirmed on X-ray.[21,22] To be included, the participants' affected joints also had to be deemed suitable for manual therapy intervention based on the presence of at least one of the following findings during the physical examination; (1) painful movement of joint; (2) limited joint range; (3) abnormal resistance to movement of the joint.[23]

Potential participants were excluded if they presented with a current hemarthrosis or an acute exacerbation of symptoms from a recent joint bleed as subjectively reported by the patient. They were also excluded if inhibitors were present (an immune response to clotting factor) or if they had undergone any change in management within the last two months including alteration of clotting factor regimen, pain medications, physiotherapy intervention, or new orthotic prescription. Exclusion was also made on the basis of concurrent diagnosis of other

forms of arthropathy such as rheumatoid arthritis, past joint replacement surgery in the affected joint, other recent surgery (within the last year) in the affected joint including synovectomy or arthroscopy, or a cognitive deficit which would preclude the ability to complete requisite questionnaires.

This research was conducted with ethical approval from the Institutional Medical Research Ethics Committee, and in accordance with the Declaration of Helsinki. All participants received verbal and written information and signed an informed consent form.

Outcome measurements

Outcome measures were performed immediately prior to and following the joint mobilization intervention. All measurements were overseen by the same investigator (E.S.).

Safety measures – adverse events (episodes of joint bleeding or exacerbations of pain)

The frequency of hemarthrosis during the last six months was recorded prior to the intervention to ensure no recent or current hemarthrosis had occurred. Over a one week period following the intervention any episodes of joint bleeding or exacerbations of pain beyond mild transient discomfort immediately following the intervention session were recorded. A one week period was considered an acceptable time frame to determine if any adverse effects from the mobilization techniques were to occur.

Measures of immediate clinical effect

Ankle and Knee Range of Motion (ROM): Passive range of knee flexion/extension, and ankle dorsiflexion/plantarflexion, were recorded in degrees using a Universal Goniometer (Large 25 cm plastic goniometer marked in 1 degree increments). Goniometry has been shown to have excellent intra-tester reliability for the measurement of knee (ICC of 0.91–0.99) [24] and ankle (ICC 0.86–0.90) [25] motion. All ROM measurements were performed in non-weight bearing and in a pain-free range to avoid potential trauma or bleeding. Each measurement was repeated over three trials and the average used for statistical analysis.

Timed Up and Go Test: During the Timed Up and Go Test [26] the participant from a sitting starting position was asked to stand and walk three meters from the chair before returning to the chair and sitting down. Two measures were recorded: (1) The TUG test – the time taken in seconds to complete the task which has shown to be a reliable measurement in an arthritic population.[27] (2) Pain during the TUG (PTUG) recorded as the patient-reported worst level of pain during the test measured on a standard Pain Numerical Rating Scale (11 point scale, ranging from 0 (no pain) to 10 (worst pain imaginable)).

Figure 1. Joint mobilization interventions. (A) talocrural dorsiflexion/plantarflexion joint mobilization applied mid-range in mild traction; (B) tibiofemoral flexion/extension joint mobilization applied mid-range in mild traction; (C) patellofemoral medio-lateral and superior–inferior (not pictured) joint mobilization.

Measures of short-term clinical effect

Lower Extremity Functional Scale (LEFS): This scale of lower limb function has 20 items, each of which the subject rates on a five-point scale (from 0 to 4 points). Questions relate to a subject's perceived ability to perform functional activities such as walking up and down stairs, putting on socks, and squatting. The LEFS has been validated in a wide range of populations, including those with osteoarthritis.[28]

Joint mobilization interventions

Joint mobilization techniques were performed on the affected ankles and knees consistent with the approach described by Maitland.[29] Techniques were applied with some individual adjustment of handling and subject positioning according to patient comfort. Treatment was applied to all knee(s) and/or ankle(s) affected by hemophilic arthropathy. All techniques were applied by the same physiotherapist (E.S.) who is experienced in implementing these interventions in this patient group.

For each affected joint, mobilization techniques were applied for three one-minute durations, separated by 10-second rest periods. The joint mobilization techniques were performed as an oscillatory movement, one cycle every four seconds. All techniques were performed as Grade 2 technique (not performed into tissue resistance or with pain provocation) according to a Maitland grading scale.[29] Participants were instructed to inform the therapist of any discomfort at which point hand position/pressure was adjusted to restore comfort. In the event that a technique could not be performed with comfort, treatment of that joint was ceased. This did not occur, however, during any of the intervention sessions.

Ankle joint mobilization consisted of pain-free, mid-range amplitude, talocrural dorsiflexion/plantarflexion performed in mild traction. This traction was applied pragmatically with some adjustment of pressure according to patient comfort (Figure 1(A)). Knee joint mobilization included two techniques. The first technique consisted of pain-free, mid-range amplitude tibio-femoral flexion/extension in mild traction (Figure 1(B)). The second

technique involved gentle superior–inferior, as well as medio-lateral, patellofemoral glides (Figure 1(C)).

Procedure

All intervention sessions were performed in a standard Hemophilia clinic conducted by the primary investigator (E.S.) at the Royal Brisbane and Women's Hospital Physiotherapy Department. This was with the exception of three sessions which were performed within the participants' own homes. This was an option offered to all potential subjects who were unable to attend the hospital in an effort to maximize recruitment. Following initial screening and informed consent procedures, participants underwent their experimental intervention session. Due to potential diurnal changes in arthritic joint pain[30], an attempt was made to standardize the sessions between 11 am and 3 pm. For the eight subjects who were unable to attend during this period, their appointments were made as close as practical to this time period.

All baseline physical measures were taken first including the Lower Limb Functional Scale, the TUG, and maximum pain during TUG (PTUG); followed by ankle and knee ROM measurements. To allow the participant's opposite leg to be used as a control for ROM measurements, the manual therapy intervention was performed in two phases. In the first intervention phase, affected joints of only the most affected limb (as identified by the subject) had mobilization techniques applied. ROM measurements were then repeated on both the treated and untreated limb, thus using the untreated side as a control. This process was then mirrored in the second intervention phase with the joint mobilization techniques now applied to the least affected limb only, before range was re-measured again on both sides. In this manner, the opposite leg acted as a non-treated control during both phases. Following completion of all joint measurements and intervention, the TUG/PTUG measures were repeated. Participants were also provided with a LEFS to be completed seven days post-intervention. Participants were also provided with the contact details of the investigator and instructed to immediately report

Table 1. Demographic and condition details of participants.

Variable	Mean (range)
Age	45 (28–67) years
Height	177 cm (166–190)
Weight	84 kg (58–116)
Sex	15 male 1 female
Knee or ankle hemarthrosis in last 6 months	1.8 (0–12)
Number of knee and ankle joints with symptomatic arthritis	2.9 (1–4)
Type of hemophilia	10 Severe A, 1 Severe Symptomatic carrier Hemophilia A, 3 Severe B, 2 Moderate A
Number on prophylactic factor replacement	4 Subjects
Arthroscopic surgery in knee or ankle	3 Subjects, between 7 and 27 years prior
Joints with full bony union	1 Knee, 1 Ankle
Total knee replacement	5 Subjects (only ankles of these individuals were included for research purposes)

Figure 2. Change in ankle dorsiflexion range following intervention to; (A) the most affected limb (phase 1), and (B) the least affected limb (phase 2).

any adverse events or concerns that may occur over the following seven days. Participants were also instructed that they should continue their usual pain medication usage over the duration of the study and to inform the investigator if pain medication usage was altered.

A follow-up phone call was made one week after the intervention session to confirm that no hemarthrosis or adverse event had occurred following the intervention, as well as to ensure the Lower Limb Functional Scale had been completed and was returned by post.

Data management and statistical analysis

Descriptive statistics (mean and standard deviation) were calculated for all measurements. Statistical analysis

was performed using SPSS (version 20). A repeated measures general linear model with Bonferroni correction for multiple comparisons was used to examine the main effects of time (pre/post intervention) for the TUG and LEFS measurements. For the ROM measurements time (pre/post intervention) $\times$ side (most affected limb, least affected limb) interaction effects were evaluated for each intervention phase. Tests for simple effects were performed *post hoc* when indicated. Statistical significance was accepted at $p < 0.05$.

Results

Participant numbers was limited by the rarity of Hemophilia. Of the 55 potential participants identified on the Australian Bleeding Disorder Registry who live within the Brisbane region, 17 were not eligible based on the study inclusion/exclusion criteria, 12 were not contactable, and 10 did not consent to participate, resulting in a sample size of 16 (29%) of the possible participants.

Participant demographic data and joint conditions are shown in Table 1. Complete bony union had occurred in the knee of one participant and the ankle of another. A further three participants had had total knee replacements. Subsequently, these joints were not assessed and treated in the study. Only 4 of the 16 subjects were on regular prophylaxis. There were no losses to follow-up.

Adverse events

There were no adverse events (episodes of joint bleeding or exacerbations of pain) reported by any participants during the seven-day period following the intervention session.

Immediate effects of intervention

Range of motion measurements

Of the 16 participants, 14 had ankle arthritis. As indicated in Figures 2(A) and 3(A) there were significant time $\times$ side interactions for both the ankle dorsiflexion ($F = 20.45$, $p < 0.001$) and plantarflexion ($F = 4.91$, $p = 0.036$) ROM measurements following intervention phase 1 (most affected side treated) with the treated side achieving significant gains in ROM in both directions compared to the untreated side.

Similarly, there were significant time $\times$ side interactions for both ankle dorsiflexion ($F = 12.52$, $p = 0.002$) and plantarflexion ($F = 6.77$, $p = 0.017$) ROM following intervention phase 2 (least affected side treated) with the treated side again achieving significant gains in ROM in both directions compared to the untreated side (Figures 2(B) and 3(B)).

In contrast, there were no significant time $\times$ side interactions in response to the manual therapy interventions (phase 1 or 2) for either knee flexion or extension range of motion ($F = 3.16$, $p > 0.106$). There was a much smaller

Figure 3. Change in ankle plantarflexion range following intervention to; (A) the most affected limb (phase 1), and (B) the least affected limb (phase 2).

Table 2. Ankle and knee range of motion Pre–post phase 1 Intervention (most affected side treated).

		Pre-intervention Mean degrees (SD)	Post-intervention Mean degrees (SD)
Most affected side	Ankle dorsiflexion (n = 14)	0.6 (11.1)	3.3 (11.8)
	Ankle plantarflexion (n = 14)	21.0 (10.4)	24.5 (11.2)
	Knee extension (n = 6)	–11.2 (11.0)	–8.4 (8.5)
	Knee flexion (n = 6)	115 (28.9)	125 (14.3)
Least affected side	Ankle dorsiflexion (n = 13)	8.2 (7.7)	7.4 (7.1)
	Ankle plantarflexion (n = 13)	26.5 (10.9)	27.5 (11.8)
	Knee extension (n = 6)	–7.6 (11.4)	–7.8 (12.0)
	Knee flexion (n = 6)	123 (18.1)	117 (30.8)

subject group for knee measures as only 6 participants had knee arthropathy. Data are summarized in Tables 2–3.

TUG measurements

There were no main effects of time (pre/post intervention) for either the TUG (Pre 11.4 ± 7.8 s, Post 11.3 ± 8.3 s, $F = 0.01$, $p = 0.92$) or PTUG (Pre 1.9 ± 2.4 , Post 1.4 ± 1.8 , $F = 1.77$, $p = 0.2$) measures.

Short-term effects of intervention

There were no main effects of time (pre/post intervention) for the LEFS (Pre 48.12 ± 18.5 , Post 49.31 ± 19.55 , $F = 0.87$, $p = 0.37$) measure. Additionally no participants

reported any change in pain medication usage over this period.

Discussion

This preliminary study observed joint mobilization techniques applied to 24 arthritic ankles and 10 arthritic knees of patients with hemophilia with no adverse events reported over the following seven days despite most subjects not being on prophylactic treatment. While this is only a small study, these are still important findings as there is limited published data describing manual therapy-related adverse events in hemophilic arthropathy. It should be noted however that these techniques were performed gently, with careful attention given to patient comfort and at a technique grade that avoided forcing the joint towards its limit of range. This application of joint mobilization is consistent with previously described clinical recommendations for these interventions.[20,21] Clinicians should consider individual variation in joint structure vulnerability during decision-making, particularly with regard to range, force and speed used in manual therapy techniques. It needs to be emphasized that the lack of adverse events in this study may not have been observed if techniques had been applied too vigorously, or within a joint range which caused excessive tissue strain. High-velocity thrust techniques (resulting in audible joint cavitation) or aggressive techniques performed at end of joint range would be contraindicated in this population with known vulnerability of joint structures.

Some immediate positive effects were observed for ankle range of motion. Ankle pain-free range of motion increased by an average of 27% after treatment of the most affected limb, and by 6% after treatment of the least affected limb. While small, these gains in range are consistent with previously reported positive effects of joint mobilization for osteoarthritis.[15–17] No significant improvement was shown for the knee range of motion; however, sample size was limited to six subjects with arthritis in their knees. Interestingly, there was no improvement in either the time or pain intensity measures during the TUG test despite the immediate gains in ankle mobility. It is worthwhile to note that a significant number of participants (6/16) scored zero for the PTUG measure before intervention. Therefore, a ceiling effect in this test may have masked potential immediate symptomatic change. Interestingly, only one participant reported an increase in their PTUG (increase in PNRS from 1 to 3) pre–post intervention. However, the participant reported the higher score was due to a single mild painful catch in his ankle while turning during the post-intervention TUG test that he often experienced in that ankle anyway. Overall while any immediate benefits were small and inconsistent, the findings suggest that no patients experienced any notable worsening of their condition from the application of the mobilization techniques.

Table 3. Ankle and knee range of motion Pre–post phase 2 Intervention (least affected side treated).

		Pre-intervention	Post-intervention
		Mean degrees (SD)	Mean degrees (SD)
Most affected side	Ankle dorsiflexion (n = 11)	4.2 (12.4)	4.0 (12.2)
	Ankle plantarflexion (n = 11)	27.0 (11.9)	24.8 (11.6)
	Knee extension (n = 5)	–8.6 (9.3)	–8.9 (10.7)
	Knee flexion (n = 5)	126 (15.9)	118 (30.1)
Least affected side	Ankle dorsiflexion (n = 11)	6.1 (7.4)	8.4 (7.7)
	Ankle plantarflexion (n = 11)	26.1 (11.8)	28.8 (13.6)
	Knee extension (n = 5)	–7.6 (13.2)	–8.5 (13.2)
	Knee flexion (n = 5)	115 (33.8)	123 (25.3)

No improvement was observed in lower extremity function (as indicated by the LEFS) over the week following intervention. This is possibly due to factors such as the severity of the presenting arthropathy and the limited effect of a single intervention session. Usual clinical practice would be to repeat manual therapy interventions over a number of sessions, and in combination with other interventions such as exercise to achieve a cumulative effect. For the purposes of this study, we chose to deliver the manual therapy intervention in a single episode to provide a clearer cause-effect platform with regard to its immediate clinical effects and potential for adverse events. However, the literature shows that for osteoarthritis, the most significant benefits of manual therapy are observed when it is combined with exercise. Improvements in pain or mobility may be better maintained when combined with exercise to facilitate longer term effects. This combined approach is also more in line with previous studies investigating conservative management of hemophilic arthropathy.[11,19]

Limitations of the study

There are significant limitations associated with this case series. Due to the rarity of eligible participants and the small available sample size, it was not feasible to have a control (not receiving treatment) or placebo (sham joint mobilization) group. Furthermore, there was no scope for blinding of outcome measures. Due to the necessity of performing the study within clinic time and with some participants seen within their home, the same investigator (E.S) conducted all outcome measures and interventions. Therefore, while changes in range were compared against an untreated control limb during both phases of intervention, we are unable to exclude the potential for bias due to a lack of blinding of the outcome measures. Furthermore, while the goniometry method used to

measure range has previously reported excellent intra-tester reliability for the knee (ICC > 0.9)[24] and ankle (ICC > 0.85),[25] we did not examine the reliability of the investigator conducting the range of motion measures in this study.

The large variation in function and pain levels between subjects in this study made selection of appropriate outcome measures difficult. For example, while it was anticipated by the investigators that higher level participants may be asymptomatic during the PTUG test, it was included as this test was deemed unlikely to be aggravating or to provoke a hemarthrosis in those with more advanced arthritis. Other limitations include the small sample size particularly for the knee. While diurnal variation of symptoms in arthritic conditions may have been another potentially confounding factor, we attempted to minimize this by undertaking sessions at similar times during the day.

Conclusions

This study provides further preliminary evidence for the safe application of joint mobilization in patients with hemophilic arthropathy. Larger scale studies are now warranted, including further safety and clinical effectiveness research for manual therapy as both an isolated and multimodal intervention. However, the findings of this study support the notion that with appropriate clinical reasoning and skillful technique, gentle manual therapy may be considered a safe and potentially effective intervention for consideration by therapists within the management of hemophilic arthropathy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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