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ORIGINAL ARTICLE

Musculoskeletal

Ankle joint distraction is a promising alternative treatment for patients with severe haemophilic ankle arthropathy

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Abstract

Introduction: Haemophilic ankle arthropathy (HAA) causes major morbidity. When conservative treatment fails, major surgical interventions are indicated. An alternative treatment to maintain joint mobility and postpone these interventions is desired.

Aim: To gather prospective data on clinical/structural changes after ankle joint distraction (AJD) in HAA.

Methods: This study includes patients with severe HAA insufficiently responding to conservative treatment. AJD was performed during 8–10 weeks by use of an external frame. Questionnaires, physical examination and radiology were used to evaluate pain, function and structural changes before and 6, 12, 24 and 36 months after distraction. Mixed effect models were used for analysis.

Results: This study includes eight cases (21–53 years). The fixed effects estimates of the visual analogue score (0–10) improved from 7.5 at baseline to 3.4 ($p = .023$) 3 years after distraction. The Haemophilia Activities List (HAL, 0–100) for basic/complex lower extremities functions improved from respectively 29.6 and 31.5 to 54.3 ($p = .015$) and 50.7 ($p = .031$). Joint mobility was maintained. Magnetic resonance imaging (MRI) showed thickened cartilage and reduced bone marrow oedema and subchondral cysts. Pin tract infections ($n = 6$) were effectively treated and no adverse bleeding events occurred. At 3-year follow-up, in none of the patients the originally indicated arthrodesis was performed.

Conclusion: This first prospective study showed that AJD in HAA results in decreased pain, improved function and decreased arthropathy-related MRI findings in the majority of patients for prolonged time. Although the study population is small and follow-up is relatively short, AJD may be promising to postpone invalidating interventions and might be a breakthrough treatment.

KEYWORDS
ankle, arthroplasty, haemophilia, joint disease

1 | INTRODUCTION

Haemophilia is characterised by spontaneous and trauma-related bleeding with the fast majority occurring in the joints and muscles.[1] Recurrent joint bleeds lead to irreversible damage, so-called haemophilic arthropathy (HA). This causes limited physical function and chronic pain and negatively affects quality of life (QoL). Treatment options are limited and preventing joint bleeds is of utmost importance. Prophylactic clotting factor replacement therapy diminished the number of bleeding events significantly, but complete prevention of joint bleeds is impossible.[2]

In adults, 60% of all joint bleeds occur in the ankle.[1] Analgesia, adequate physical therapy, optimal recovery after a joint bleed, orthotics and synovectomy can be effective in early stages of haemophilic ankle arthropathy (HAA), but more invasive treatments are required when these treatments fail. Joint fusion (arthrodesis) is effective in pain relief, reducing recurrent joint bleeds and correcting deformity. Nevertheless, complete loss of mobility of the joint and increased weight-bearing on adjacent joints result from this procedure.[3,4] An alternative option is total ankle replacement (TAR). This treatment remains controversial because of the concern of deep infections and aseptic loosening. The mean age of the haemophilia population needing joint surgery is about 20 years lower than of other patients with joint diseases.[5,6] Young patients are considered at high risk for revision surgery due to a higher activity level and more intensive use of the joint.[7] Moreover, costly and less effective revision therapy is usually required between 10 and 20 years after implantation and results of this surgery are in general poor.[8,9] A last resort intervention is lower limb amputation, having a huge impact on QoL and participation in the society. Obviously, there is a need for alternative treatments to postpone these major interventions.

In osteoarthritis (OA), a joint disease with similar degenerative features as HA,[10] a significant and prolonged clinical benefit was observed after ankle joint distraction (AJD). During AJD, the lower tibia and talus are temporarily fixed to an external frame and 5 mm of distraction is applied.[11,12] This surgical approach utilises the idea that damaged joint cartilage can partly regenerate itself when there is reduced mechanical loading, initiating joint tissue repair.[13] AJD in OA resulted in a strong decrease in pain and improvement in function in almost three quarter of the patients.[11] These results were further supported by the studies with larger groups of patients with knee OA treated with distraction in which magnetic resonance imaging (MRI) and biochemical markers revealed structural changes pointing at a regenerative process upon treatment.[14]

AJD has already been performed in our centre in three patients with HAA to prove feasibility. Retrospective evaluation showed evident clinical and structural improvements.[15] However, prospective data on the clinical efficacy and tissue structure changes of AJD in HAA are not available. As such, we performed the first prospective study to investigate whether AJD in HAA leads to improvement in pain and function and structural changes. To assess the long-term outcomes, we also included the retrospective evaluation of three patients treated with AJD before.

2 | MATERIALS AND METHODS

2.1 | Patients

This prospective single arm exploratory interventional study included patients with haemophilia A/B aged 18–55 years with severe complaints of HAA in primarily the tibiotalar joint, insufficiently responding to conservative treatment and resulting in functional limitations. When surgical intervention was indicated, AJD was offered to the patient. Exclusion criteria were contra-indications for surgery or MRI examination, complaints of the ankle primarily due to arthropathy in the subtalar joint, inability to wear a distraction frame for 10 weeks due to psychological issues, absence of any joint space on the X-ray or a history of inflammatory/rheumatoid arthritis in the affected ankle.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethical Committee of the University Medical Center Utrecht (13-193). All patients gave written informed consent.

2.2 | Ankle joint distraction

Patients were treated according to standard practices protocols for AJD as used previously in OA studies.[11] The procedure was performed under general anaesthesia with administration of antibiotics (cefazoline for 24 h) pre- and post-surgery and continuous clotting factor infusion during 7 days. An external fixation frame was placed around the ankle (Figure 1) and distraction was performed during surgery and thereafter twice a day until a total distraction of 5 mm was achieved. The procedure is described in detail in Supplementary File 1.

At day 5 the distraction was checked on a weight bearing X-ray and adapted if necessary. Patients were discharged at day 7 and they received additional prophylactic clotting factor substitution for 1 week and returned to their normal schedule at week 2. X-ray evaluation of the distraction and wound control were performed 2–3 weeks after surgery. At 10 weeks, the distraction frame was removed under general anaesthesia after clotting factor substitution. Patients were discharged the same day and gradually regained normal full loading and range of motion (ROM), guided by a specialised physiotherapist (P.K.). In three cases, an anterior osteophyte was removed with an osteotomy at the time of application of the frame. This procedure, called nettoyage, is supposed to cause a weight shift from the area with cartilage damage to an area with more healthy cartilage. It was performed based on the opinion of the orthopaedic surgeon.

2.3 | Clinical evaluation

Clinical evaluation was performed just before distraction and 6, 12, 24 and 36 months after distraction. Improvement over time was assessed by different questionnaires. Change in pain was measured by the Visual Analogue Scale (VAS), a well-known general, not ankle specific, pain score with a 10 cm line depicting the level of pain (10 being the worst

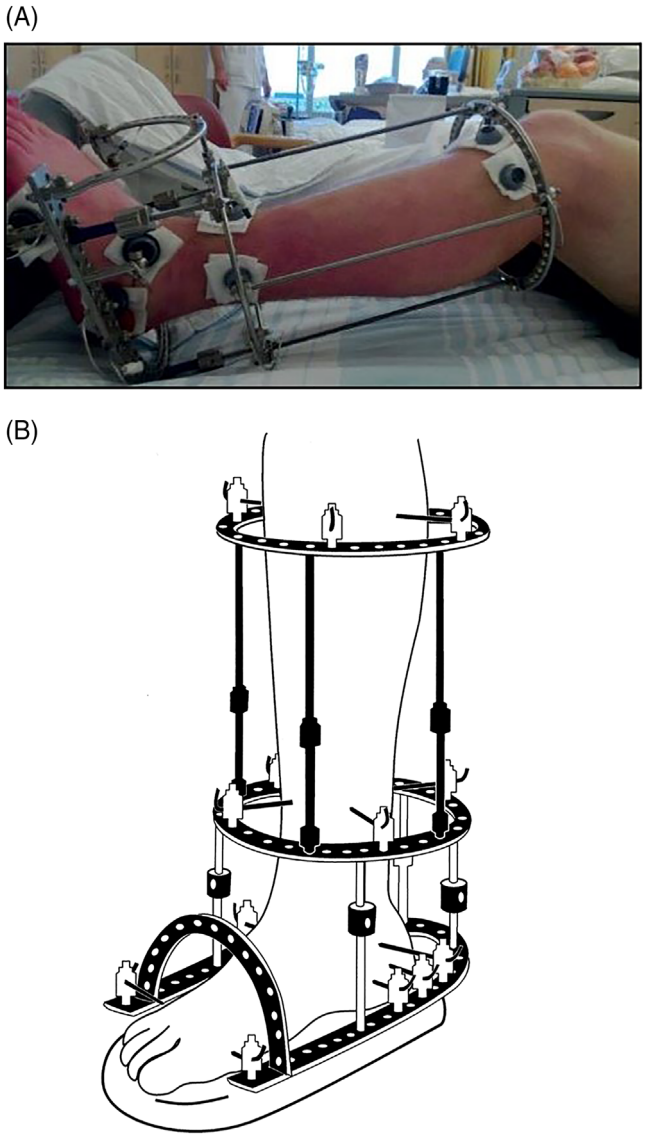

FIGURE 1 (A) Ankle joint distraction frame. (B) Graphic illustration ankle joint distraction frame

score). In addition, pain was measured by the Ankle Osteoarthritis Scale (AOS), a questionnaire validated for ankle OA and also used for orthopaedic interventions in haemophilia (100-point scale, 100 being the worst pain score).[16] Ankle specific functioning was measured by the AOS disability score (a 100-point scale, 100 being the worst score). The Haemophilia Activities List (HAL, a 100-point scale, 0 being the worst score) was used to assess self-perceived functional health.[17,18] The Goal Attainment Scale (GAS), a 6-point scale from −3 to +2, was used to measure individual milestones objectively and to enable scoring on group level.[19,20]

2.4 | ROM and performance tests

ROM (dorsal and plantar flexion) of both ankles was measured as full arc of mobility of the tibiotalar joint by an experienced physiotherapist (P.K.) using a goniometer. This measurement was based on the ROM items in the Haemophilia Joint Health Score.[21]

Also, the figure-8 walking test both at preferred and maximum speed, the 50-m walking test at preferred speed and the 6-min walking test were carried out. During the figure-8 walking test the patient walks around two cones which are placed 8 m apart from each other, forming an *eight figure*. This test was performed at both preferred and maximum speed and the result was the total time in seconds required to complete the figure. During the 50-m test the patient walks 50 m at preferred speed from a starting point towards a designated point in a straight line. In the 6-min walking test, the patient walks as far as he can during 6 min on a 35 m track in a gym of which the total distance walked in 6 min is the main outcome.[22–24]

2.5 | Structural evaluation

Structural changes were determined by radiography and MRI and assessed by an experienced radiologist (W.F.) in blinded way using validated scores in addition to a summarised impression of changes over time for each case. X-rays were performed in two directions under full weight-bearing and scored according to Pettersson score (PS) for HA evaluating subchondral bone changes and joint space width.[25,26] MRI was performed before distraction and at 1 and 3 years after distraction. MRIs were performed in three directions including T1, T2 and proton-density weighted sequences. They were assessed by the additive International Prophylaxis Study Group (IPSG) MRI score, especially specific for the early detection of joint disease in haemophilic patients.[27,28] Higher scores on these imaging studies reflect more arthropathy.

2.6 | Long-term evaluation

To assess the long-term outcomes in patients who underwent AJD, the patients ($n = 3$) previously studied by Van Meegeren et al. were invited for follow-up investigations, performed during a routine outpatient clinic visit.[15] These patients are different from the ones investigated in our prospective study. To evaluate the clinical outcomes, we used the same questionnaires as used previously in these patients: HAL, impact on participation and autonomy (IPA) list and the Van Valburg questionnaire. The IPA questionnaire evaluates impact of chronic disability on participation and autonomy.[29–31] The Van Valburg questionnaire evaluates clinical condition, ROM, function and pain. Also, X-rays were performed to assess the structural changes and scored by the same radiologist (W.F.) using the PS.

2.7 | Statistical analysis

The longitudinal data were tested for normality of the residuals and homoscedasticity. Log transformations were performed to evaluate if results were comparable. Mixed effect models were used to

TABLE 1 Demographics

	Haemophilia type	Clotting factor	Clotting factor regime	Duration distraction (weeks)	Ankle	Age at distraction (year)	Weight (kg)	Length (cm)	Nettoyage	Follow-up (months)
AJD 1	B	<1%	OD	10	Left	21	84	182	No	36
AJD 2	A	<1%	PL	10	Right	25	125	192	No	36
AJD 3	A	<1%	PL	10	Right	32	91	184	No	24
AJD 4	*A*	*<1%*	*PL*	*10*	*Left*	*33*	*90*	*190*	*No*	*36*
AJD 5	A	<1%	PL	8	Left	21	77	187	No	36
AJD 6	A	2%	OD	10	Left	45	88	191	Yes	36
AJD 7	A	<1%	PL	10	Right	53	83	184	Yes	36
AJD 8	*A*	*<1%*	*PL*	*10*	*Right*	*38*	*90*	*190*	*Yes*	*36*

Italics: same patient. AJD, ankle joint distraction; OD, on demand; PL, prophylaxis.

analyse baseline and follow-up data. This analysis was chosen to analyse repeated measurements within a patient and to deal with missing values in this small patient population. Outcomes were also expressed as z-scores and the mixed effect model analysis was repeated using these scores to obtain effect estimates as effect sizes. Analyses were performed using IBM SPSS Statistics version 26 (IBM, SPSS, Armonk, NY, USA) and graphics were made with GraphPad Prism version 8.3 (GraphPad Software, San Diego, CA, USA). *p*-values < .05 were considered as statistically significant. In accordance with the article by Van Meegeren et al., mean scores were calculated for pain and function in the three additional retrospective patients.[15]

3 | RESULTS

Currently, we present the 3-year follow-up data. In total, eight AJDs were performed, of which one patient received joint distraction in both ankles with 4.5 years interval. All patients completed the 3-year follow-up, except for one patient who was lost to follow-up 24 months after his distraction. In three patients, AJD was combined with nettoyage. Demographics are summarised in Table 1.

3.1 | Adverse events

There were no bleeding events during the application procedure and the distraction period. Six patients experienced a superficial pin tract infection, commonly seen with external frames. These were all successfully treated with a short course of antibiotics. In one patient, the complete distraction was achieved gradually over 5 days instead of 3 days, as the initial first 2 mm of distraction could not be performed during application surgery due to too much pain. One patient was admitted to the hospital 8 days after the procedure for additional pain medication because of knee pain after an accident with a slipping crutch. Two patients were diagnosed with reactive synovitis in the affected ankle 1 year post-operatively and treated with celecoxib. In both patients, synovitis was also seen on MRI before the distraction.

3.2 | Pain

Figure 2 shows the individual VAS and AOS pain scores over time. Both scores showed a downward trend after AJD. To assess the clinical relevance of this decrease in pain, the patient acceptable symptom state (PASS), a value beyond which patients consider themselves as well, is used. In patients with knee and hip OA, the PASS VAS score was 3.2–3.5. In our patient population, pain measured by the VAS score (Figure 2A) was already statistically significantly lower after 6 months and further decreased during the remaining follow-up towards the PASS value.[32] The AOS pain score (Figure 2B) showed a similar trend for improvement immediately after AJD, though this was statistically significant at 3 years. No differences in pain levels were observed in patients with and without nettoyage. In the patient that underwent AJD in both ankles, at 3-year follow-up of the first ankle, his general pain score (VAS) was 95% of the maximum score. However, this was caused by pain of his still untreated ankle as the AOS pain score, which is ankle specific, was 9.4% of the maximum score.

3.3 | Function

Functionality is reflected by the HAL questionnaire. This questionnaire consists of three domains: functionality of the upper extremities and basic and complex functionality of the lower extremities. As expected, the functionality of the upper extremities did not show any significant difference after AJD. The HAL scores for both the basic and complex lower functions (Figure 3A, B) increased statistically significantly post-treatment, showing that patients gradually regain the functions of the affected ankle and that improvement in the basic functions precedes that of the complex functions. Again, no significant differences in HAL scores were observed for patients with and without nettoyage. When assessed by the AOS function score, a comparable functionality improvement was seen. This score statistically significantly decreased after the distraction (Figure 4).

All patients showed an increase in GAS score 1 year after distraction, except for one patient suffering from reactive synovitis and pain.

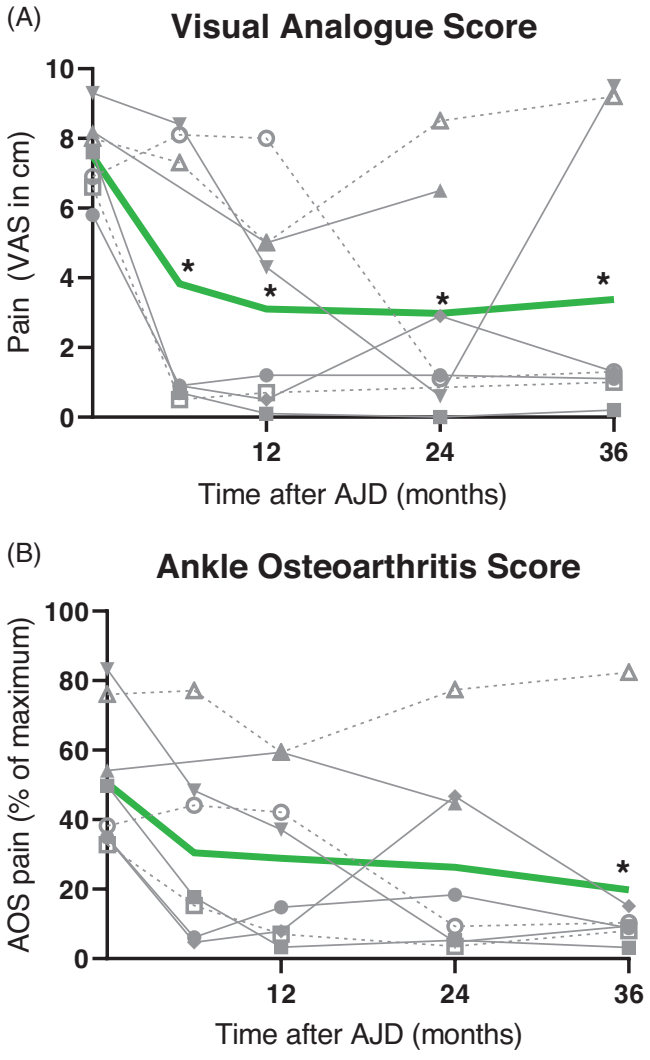

FIGURE 2 (A) Longitudinal individual pain scores ($n = 8$). The green line represents the fixed effects estimates derived from the mixed effect model. Dotted lines represent patients with nettoyage ($n = 3$). * = Statistically significant. Baseline ($n = 7$); 6 months ($n = 7$); $p = .041$; 12 months ($n = 8$); $p = .013$; 24 months ($n = 7$); $p = .013$; 36 months ($n = 7$); $p = .023$. Effect estimates: the differences from VAS baseline in outcome were −3.15, −3.78, −3.89 and −3.55 at time point 6, 12, 24 and 36 months after distraction. (B) Longitudinal individual pain scores ($n = 8$). The green line represents the fixed effects estimates derived from the mixed effect model. Dotted lines represent patients with nettoyage ($n = 3$). * = Statistically significant. Baseline ($n = 8$); 6 months ($n = 7$); $p = .133$; 12 months ($n = 8$); $p = .094$; 24 months ($n = 8$); $p = .062$; 36 months ($n = 7$); $p = .023$. Effect estimates: the differences from AOS pain baseline in outcome were −1.02, −1.10, −1.23 and −1.57 at time point 6, 12, 24 and 36 months after distraction. AJD, ankle joint distraction; AOS, Ankle Osteoarthritis Scale; VAS, Visual Analogue Scale

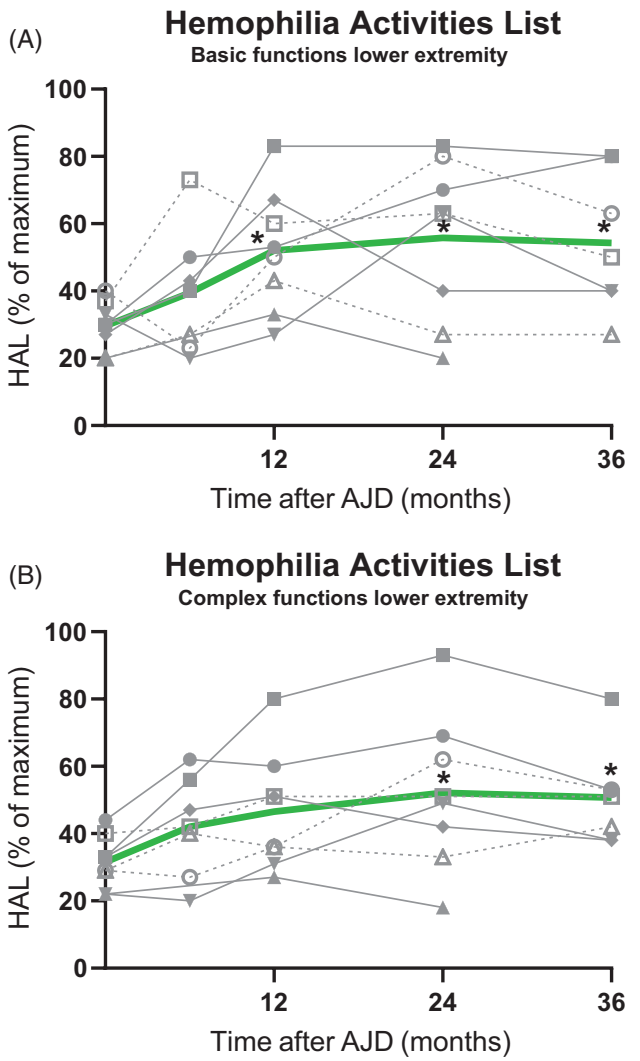

FIGURE 3 (A) Longitudinal individual HAL scores ($n = 8$). The green line represents the fixed effects estimates derived from the mixed effect model. Dotted lines represent patients with nettoyage ($n = 3$). * = Statistically significant. Baseline ($n = 8$); 6 months ($n = 7$); $p = .314$; 12 months ($n = 8$); $p = .021$; 24 months ($n = 8$); $p = .008$; 36 months ($n = 7$); $p = .015$. Effect estimates: the differences from HAL baseline in outcome were 1.36, 3.09, 3.61 and 3.41 at time point 6, 12, 24 and 36 months after distraction. (B) Longitudinal individual HAL scores ($n = 8$). The green line represents the fixed effects estimates derived from the mixed effect model. Dotted lines represent patients with nettoyage ($n = 3$). * = Statistically significant. Baseline ($n = 8$); 6 months ($n = 7$); $p = .226$; 12 months ($n = 8$); $p = .077$; 24 months ($n = 8$); $p = .017$; 36 months ($n = 7$); $p = .031$. Effect estimates: the differences from HAL baseline in outcome were 1.35 1.92, 2.64 and 2.46 at time point 6, 12, 24 and 36 months after distraction. AJD, ankle joint distraction; HAL, Haemophilia Activities List

After 3 years, two patients did not achieve their predefined goal. One patient was at the same score compared to baseline (−2) and another patient had a score of −1, indicating that there was an improvement but this did not reach the desired improvement as defined pre-surgery. One patient reached the goal that was initially set by the patient and the clinician and four patients had a GAS score of 1 or 2, indicating that they achieved a goal that was beyond what was initially expected.

3.4 | ROM and performance tests

The ROM (full arc of mobility) was maintained after AJD. Table 2 shows the mean and range ROM values. Supplementary File 2 displays the

TABLE 2 ROM (mean and range) and performance tests (median and interquartile range)

	Baseline ($n = 8$)	After 1 year ($n = 8$)	After 3 years ($n = 7$)
ROM	39° (30°–50°)	40° (24°–55°)	44° (30°–60°)
Figure 8 at preferred speed (s)	15.4 (13.33–17.79)	14.0 (11.95–14.95)	13.5 (12.03–15.50)
Figure 8 at maximum speed (s)	10.9 (10.59–12.61)	10.3 (8.79–11.81)	10.5 (8.37–11.37)
Walking test 50 m (s)	33.7 (30.06–37.30)	28.9 (27.15–34.40)	30.5 (27.13–31.70)
6 Min walking test (m)	552.5 (440–560)	573.5 (515–652.50)	570.0 (525–605)

ROM, range of motion.

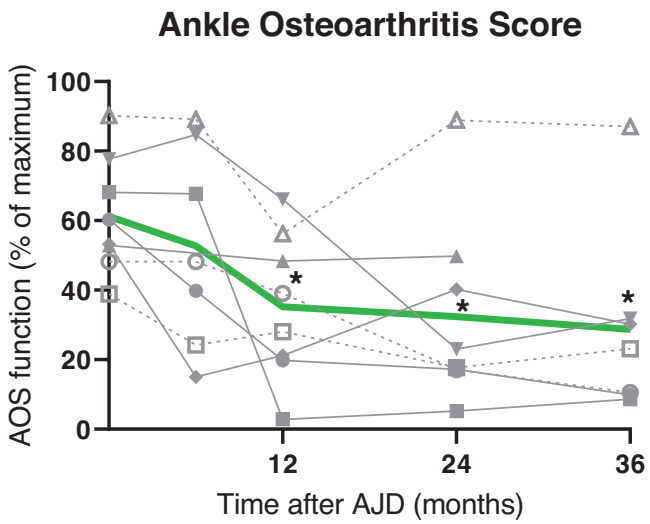

FIGURE 4 longitudinal individual AOS function scores ($n = 8$). The green line represents the estimates derived from the mixed effect model. Dotted lines represent patients with nettoyage ($n = 3$). * = Statistically significant. Baseline ($n = 8$); 6 months ($n = 7$); $p = .482$; 12 months ($n = 8$); $p = .031$; 24 months ($n = 8$); $p = .017$; 36 months ($n = 7$); $p = .010$. Effect estimates: the differences from AOS function baseline in outcome were −.51, −1.55, −1.72 and −1.94 at time point 6, 12, 24 and 36 months after distraction. AJD, ankle joint distraction; AOS, Ankle Osteoarthritis Scale

individual values of the ROM. Full arc of mobility was not different between patients with and without nettoyage.

Regarding the performance tests, on average an improvement of speed or distance was seen which sustained over time. Patients with and without nettoyage showed no significant differences in performance tests (Table 2).

3.5 | Structural changes

Structural changes following AJD were assessed with X-ray and MRI. Table 3 shows the median Pettersson and IPSG subscores. Supplementary File 3 shows the individual scores. Figure 5 shows the structural changes on MRI. Clear structural improvements like a decrease in subchondral cysts and oedema and an increase in cartilage thickness on MRI (e.g., case 1, 2, 3, 7) were not always reflected by a decrease/improvement of the IPSG MRI score.

3.6 | Long-term evaluation

We evaluated three additional patients who underwent AJD 11–13 years ago. These patients were studied before by Van Meegeren et al. 1.7–3.4 years after AJD. None of these patients had undergone ankle surgery afterwards. Table 4 summarises the results of this evaluation. Supplementary File 4 shows additional individual data.

4 | DISCUSSION

This is the first study prospectively evaluating AJD in HAA. Three-year follow-up of eight AJD procedures in seven patients showed substantial clinical improvements in pain (measured with VAS and AOS pain score) and function (measured with AOS function, HAL questionnaires, GAS and physical examination). These clinical improvements were accompanied by structural changes like decreased oedema and subchondral cysts and thickened cartilage seen on X-ray and MRI. It is also important to note that mobility of the joint was maintained and that no adverse bleeding events occurred. The procedure was frequently complicated by pin tract infections, but these were all treated with a short course of antibiotics. Furthermore, in none of the patients the originally indicated arthrodesis, which would have resulted in complete loss of ankle joint mobility, was performed.

There are no clearly established criteria before proceeding to invasive procedures like arthrodesis and AJD. Therefore, it is important to set pre-defined goals, enabling the patient and the physician to assess whether the treatment was successful. The GAS evaluates the progress that is made on individual level and in this way, aids in determining whether the treatment was successful. In a young and active patient population undergoing total knee arthroplasty, goal-specific and personalised rehabilitation using GAS resulted in higher patient satisfaction with work activities compared with standard rehabilitation, 1 year after the surgery.[33] In our study, we found that at 3-year follow-up, all patients, except for one, showed improvement and four out of seven patients achieved a goal that was beyond what was defined pre-surgery.

TABLE 3 Pettersson scores (X-ray) and IPSG scores (MRI) at baseline and 1 and 3 years after AJD (median + interquartile range)

IPSG MRI	Baseline ($n = 8$)	1 year ($n = 8$)	3 years ($n = 7$)
Soft tissue	1.0 (.0–2.8)	.5 (.0–2.0)	.0 (.0–2.0)
Osteochondral	6.5 (6.0–7.0)	6.0 (4.3–7.8)	6.0 (5.0–7.0)
Total	8.0 (6.3–9.8)	7.0 (5.5–9.8)	7.0 (6.0–10.0)
PS	6.0 (5.3–6.8)	6.0 (5.3–6.0)	6.0 (5.0–7.0)

AJD, ankle joint distraction; IPSG, International Prophylaxis Study Group; MRI, magnetic resonance imaging; PS, Pettersson score.

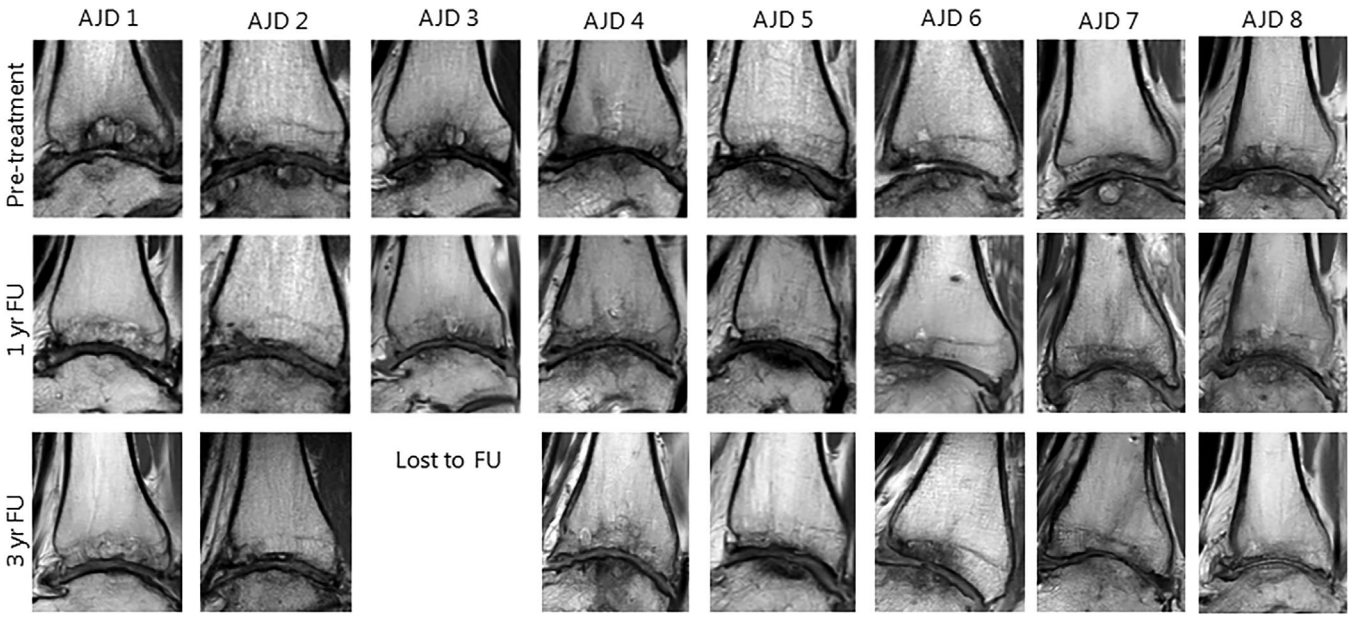

FIGURE 5 Magnetic resonance imaging (MRI) slides with decreased oedema, less subchondral cysts and thickened cartilage

TABLE 4 Patient characteristics and mean scores at follow-up

Patient characteristics			
	Retrospective patient 1	**Retrospective patient 2**	**Retrospective patient 3**
Years after distraction	12.9	11.9	11.6
Age at distraction (year)	18	33	29
Type of haemophilia + severity (factor level)	Severe haemophilia A (<1%)	Moderate haemophilia B (2%)	Mild haemophilia A (10%)
Mean scores at follow-up			
	Pre-distraction	**1.7–3.4 years after AJD**	**11–13 years after AJD**
Pain score (0–10)	8.0	2.3	4.0
HAL lower extremity basic functions	19.0	58.0	61.0
HAL lower extremity complex functions	26.0	60.0	54.7

AJD, ankle joint distraction, HAL, Haemophilia Activities List.

Follow-up will be extended to 10 years to further elucidate the long-term effects of AJD. In patients with severe OA treated with AJD, 73% of the patients had a significant and clinically relevant improvement that was maintained for at least 7 years.[34,35] In patients with OA and knee joint distraction (KJD), 9-year survival of the native knee was demonstrated for 72% of the men treated. Women had a lower chance of survival. However, this is not relevant for our population as HA only affects males.[36] Considering that the pathophysiology of HA shares similarities with that of OA, specifically regarding degenerative aspects, we speculate that the long-term benefit seen in patients with OA will be similar in patients with HAA. However, as patients with haemophilia are likely to experience joint bleeds after their distraction as well, it is important to monitor the long-term effects in this specific patient population. To provide a first insight in the

long-term effects of AJD in HAA, we studied three patients who underwent AJD 11–13 years ago. Although all patient data before the procedure were acquired retrospectively, these three patients reported a satisfactory pain and function level 11–13 years after distraction. Importantly, conservative treatments failed in these patients and without AJD, arthrodesis was the only option left. Thus far, none of these patients has undergone arthrodesis. This suggests that AJD can postpone arthrodesis with subsequent loss of ROM and potential overload of other joints.

The underlying mechanisms involved in the observed benefits after joint distraction are not fully elucidated. One explanation is that the combination of reduced mechanical stress and maintained intermittent changes in hydrostatic pressure is important for the nutrition of chondrocytes. This leads to the stimulation of proteoglycan synthesis and a decrease in pro-inflammatory cytokines. Also, the attachment of mesenchymal stem cells to cartilage is increased, further contributing to cartilage repair.[37–40] Moreover, the distraction frame takes over mechanical stress on bone resulting in transient peri-articular osteopenia and this leads to significant changes in bone turnover and may provide growth factors.[13] A canine model revealed an altered chondrocyte metabolism indicating that the chondrocyte function was normalised by distraction.[37] Understanding of the different processes taking place is improving and this may lead to more targeted treatment options and can help in selecting the patients most benefitting from this treatment and optimising treatment conditions.

AJD is an intense treatment and therefore not suitable for every patient. Patients are admitted to the hospital for 1 week and receive continuous clotting factor infusion. They wear a frame for up to 10 weeks hampering night rest, dressing, mobility and daily activities. Also, after removal of the frame, patients need to gradually regain their mobility with long-lasting physiotherapy. Moreover, patients can experience pin tract infections, something which is commonly seen with external frames and requires antibiotics.[35] A recent study by Jansen et al. showed that in OA patients treated with KJD the use of cadexomer iodine ointment resulted in a significant reduction of the number of patients suffering from pin tract infections.[41] Incorporating this antimicrobial ointment in future studies involving patients with AJD can improve the experience of the procedure. A specific concern in haemophilia patients is the risk of bleeding. With adequate clotting factor substitution, no bleeding complications were observed.

4.1 | Limitations

This study also has some limitations. We used questionnaires to assess pain and functionality and this can lead to response bias, but these questionnaires are also used to select patients eligible for surgery in daily practice. Also, the intensive physiotherapy guided by a specialised physiotherapist after AJD will probably improve ROM. However, improvement in ROM is not a goal on itself for this treatment. If we compare AJD with the alternative treatment arthrodesis, patients lose complete joint mobility and physiotherapy cannot improve this. The ROM measurements in this study illustrate that with AJD, ROM is at least maintained. Also, there was no difference in ROM between patients with and without resection of osteophytes (Supplementary File 2). Further, this study had a small sample size and included one patient with AJD in both ankles and one patient who was lost to follow-up after 24 months. Levels of significance should be interpreted with caution because of this small sample size, especially in the sub-analysis for nettoyage ($n = 3$). Mixed effects models were used to analyse our data and to deal with multiple measurements and missing data. Furthermore, this study had a follow-up of 3 years. Although the effects after AJD are long-lasting in patients with OA and our three retrospective patients, we will continue this prospective study to determine if the benefits are indeed long-lasting. We tried to provide a relatively complete overview of the effectiveness of AJD by examining both clinical and structural improvements. It turned out that AJD does not always improve the results of the PS, as two patients had an increase in PS. On the other hand, clear structural improvements seen on MRI, like changes in subchondral cysts and cartilage thickness, are not always reflected by changes in scores. MRI scores for HA have especially been used to evaluate early joint disease in a semi-quantitative manner. However, in moderate-severe arthropathy, a ceiling effect may be present resulting in no/minor changes in the score when changes occur after a certain stage of arthropathy. These scores might therefore not be useful for regeneration follow-up and more dedicated scoring of cartilage and subchondral cysts may be required.

In patients with end-stage knee OA treated with KJD, cartilage in the weight-bearing region was significantly thicker 1 and 2 years post-treatment compared to pre-treatment as determined by MRI analyses. It became gradually thinner after 5- and 10-year follow-up, but was still increased as compared to baseline.[42] Also, in patients with advanced post-traumatic ankle OA treated with AJD, the resolution of subchondral bone cysts and normalisation of bone density was correlated with clinical improvement.[14] Anyhow, the aim of AJD is primarily to reduce pain and improve function.

In conclusion, AJD has potential in the treatment landscape of HAA. Patients undergoing AJD showed improvements in pain, function and tissue structures. Importantly, dorsal and plantar flexion of the joint was maintained. As such, AJD is an attractive alternative to arthrodesis and TAR. It has the ability to postpone these major interventions which greatly impact QoL and participation in the society, especially in this young and active patient population. Moreover, arthrodesis and TAR are still possible after AJD. We will continue with the follow-up to confirm the assumptions about the long-term effects and also include more patients in the future.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

E.D.P. van Bergen: formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualisation, project administration. S.C. Mastbergen: writing – formal analysis, review & editing, supervision. H.C. Vogely: methodology, investigation. P. de Kleijn: investigation. T.N. Balani: formal analysis, writing – review & editing, visualisation. W. Foppen: formal analysis, investigation. P.M. van Roermund: methodology, investigation. F.P.J.G. Lafeber: writing – review & editing, supervision. R.E.G. Schutgens: conceptualisation, methodology, supervision, funding acquisition, writing – review & editing, supervision. L.F.D. van Vulpen: conceptualisation, methodology, formal analysis, investigation, resources, data curation, writing – review & editing, supervision, project administration.

DATA AVAILABILITY STATEMENT

Dedicated databases were used for processing and analysing the data. E.D.P. van Bergen and T.N. Balani analysed that data under supervision of an epidemiologist (P.W.). All authors had access to primary clinical trial data. The original data is not yet publically available as this study is still ongoing. The deidentified patient data will come available after the last follow-up visit (2028). For questions regarding the original data, study protocol, statistical analysis plan or informed consent forms, please contact the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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