Intraarticular management of chronic haemophilic arthropathy (Review)

DANIELA POENARU[1], MIRUNA IOANA SANDULESCU[2] and DELIA CINTEZA[1]

[1]Rehabilitation Department; [2]Doctoral School, Carol Davila University of Medicine and Pharmacy, Bucharest 020021, Romania

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Abstract. Hemophilia is an inherited X-linked bleeding condition with predominant joint involvement due to intra-articular bleeding, hemosiderin deposition and the synovial hypertrophy that is responsible for cartilage destruction, joint deformity and malalignment, pain and functional restriction. Management of chronic arthropathy includes conservative and surgical approaches. Conservative therapies consist of pain modulation, oral drugs, physiotherapy and intra-articular agents. For the present review, the literature was searched for intra-articular agents and 20 papers on the use of corticosteroids (CS), hyaluronic acid (HA) and platelet-rich plasma (PRP), with different regimes of administration, were included. CS had a longer record of injection, with statistically significant pain reduction and functional improvement in the short-term and moderate persistence in the long-term. HA was able to improve the clinical and functional status of joints with moderate or severe hemophilia. PRP was relatively recently introduced to joint management and the results remain controversial. Different associations between the above-mentioned agents were proposed by studies including a small number of patients, producing comparable results. It was concluded that there is a need for extensive research on intra-articular agents, with stratification according to the severity of joint involvement. The lack of a blinded or placebo-controlled arm due to ethical aspects makes the task challenging.

Contents

Correspondence to: Dr Daniela Poenaru, Rehabilitation Department, Carol Davila University of Medicine and Pharmacy, 37 Dionisie Lupu Street, Bucharest 020021, Romania
E-mail: daniela.poenaru@umfcd.ro

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1. Introduction

Haemophilia represents an inherited pathological condition that is X-linked; it is a bleeding disorder due to low levels of clotting factors: Factor VIII for type A and factor IX for type B. According to the circulating levels of clotting factor, the condition may be severe (<1%), moderate (1-5%) or mild (>5%).

Prophylactic and therapeutic administration of clotting factors have changed the clinical evolution and life quality of the haemophilic patient. It was presumed that early administration of clotting factors (between years 1 and 2 of age) may prevent or alleviate the development of joint pathology. However, this was not always the case, due to various factors (socio-economic and familial factors, inhibitor development, recurrent trauma).

In the long term, bleeding into the joints is the common clinical manifestation, affecting ankles, knees and elbows. Intra-articular bleeding leads to hemosiderin deposits into the synovium. Intra-articular iron and cytokines (IL-1, TNF-α) have major roles in chronic proliferative synovitis, hypervascularity, cartilage damage and bone destruction.

Chronic haemophilic arthropathy features a swollen joint, with synovial hypertrophy and marginal bony production, malalignment, reduced mobility and chronic pain. Several classification systems have been proposed to quantify and monitor the severity of arthropathy based on clinical and imagistic findings.

Clinical findings of the physical and functional examination were included in several scoring systems. In clinical settings, an early scoring system based on the severity of arthropathy displays 4 grades. Grade I: Transitory synovitis with no post-bleeding sequel; the joint goes back to the pre-bleeding stage once the hemarthrosis has subsided. Grade II: Permanent synovitis with joint enlargement, synovial thickening and limitation of movements. Grade III: Chronic arthropathy-in addition to the symptoms of grade II, there are axial deformities and muscle atrophy. Grade IV: Fibrous or bony ankylosis (1).

In 1977, Arnold and Hilgartner (2) proposed a classification of knee haemophilic arthropathy based on plain radiograph. Stage 0: Normal joint; stage I: No skeletal abnormalities, soft-tissue swelling is present; stage II: Osteoporosis and overgrowth of the epiphysis, no cysts, no narrowing of the cartilage space; stage III: Early subchondral bone cysts, squaring of the patella, widened notch of the distal femur or humerus, preservation of the cartilage space; stage IV: Findings of stage III, but more advanced; narrowed cartilage space; stage V: Fibrous joint contractures, loss of the joint cartilage space, extensive enlargement of the epiphyses with substantial disorganization of the joint (2). Conventional X-ray was also used for the Pettersson score (1980) and covers 8 items with a total of 13 points. Severe cases score 0-3 points, moderate 4-8 and mild >9 (3). Magnetic resonance imaging (MRI) is a more sensitive tool to detect changes in the joint; various scoring systems were developed and they need standardization (4). Ultrasound examination (gray-scale and color Doppler) has advantages in terms of costs, availability and accessibility and is able to identify synovial hypertrophy and hypervascularity. Since 2006, the Haemophilia Joint Health Score is largely accepted. It scores 3 joints bilaterally (elbow, knee, ankle) and gait, with values up to 124 (the higher the score, the worse).

Chronic arthropathy is subject to conservative and surgical management. Conservative therapies are the first option aiming to reduce intra-articular bleeding and provide pain control and functional improvement. Conservative measures include physiotherapy, oral drug administration for analgesia and intra-articular administration of various agents. Synovectomy, excision or destruction of hypertrophic synovium, may be performed through different modalities: Open surgery, arthroscopic, radionuclide or chemical intervention. Surgical therapies may be explored after the failure of conservative measures and following a thorough evaluation (5).

The present study focused on intra-articular injection of agents to reduce pain, to improve the functional status and to increase the quality of life. The interest toward this method arose in the early 1990 and grew as new technologies came into being. Beginning with corticosteroids (CS) and advancing to hyaluronic acid (HA) and platelet-rich plasma (PRP), researchers studied different protocols. The rationale of intra-articular treatments lies in the assumption that advanced haemophilic arthropathy is similar to idiopathic osteoarthritis, although it is clear that the pathologic mechanisms differ.

2. Methods

A literature search of studies published until January 2023 was performed in the electronic databases PubMed/Medline (https://pubmed.ncbi.nlm.nih.gov/) and Cochrane Library (https://www.cochranelibrary.com/) and using the Google Scholar search engine, with the following MeSH terms: Intra-articular injection AND haemophilia. Two independent authors (DP and DC) extracted a total of 280 papers, written in the English language, with available abstracts. After excluding duplicates, 134 papers were examined. Papers containing meta-analyses and narratives were removed, as well as studies on cell cultures and animal models (Fig. 1).

The final research focused on 20 papers, which were grouped in terms of the following topics: HA, PRP, CS, combined therapies and comparative studies (summary, see Table I).

Of the 20 studies analyzed (1,6-24), 17 were prospective, two were retrospective (7,16) and one had two arms, prospective and retrospective (14). A total of 17 studies were available as full-texts and 3 were only available as abstracts (7,17,18); however, it was possible to extract the main data to include them in the current study. In addition, two articles were pilot studies (6,24) and 4 were case series (12,13,15,20). None of the studies, except for one (22), were placebo-controlled studies due to moral considerations, as stated by the authors.

All of the papers reported prophylactic factor replacement, considering intra-articular injection as a minor surgery for haemophiliacs. The aim was to increase the patients' factor level to 50% immediately before and 24 h after the injection. Under these conditions, the bleeding risks are reduced and the safety of the procedure is assured, as stated in all of the papers.

As the main agent for intra-articular injection, 4 papers (109 joints) followed exclusively CS administration (6,7,8,14), 7 studies (196 joints) HA (1,9-11,18,21) and 3 studies PRP (243 joints) (13,16,22). A total of 2 papers focused on CS plus HA (55 joints) (15,17) and 2 papers on HA plus PRP (48 joints) (20,23). Furthermore, one paper compared HA with PRP (22 joints) (19). The severity of arthropathy was mild to moderate in one study (21 joints) (21) and moderate and severe in 4 papers (127 joints) (1,10,15,17); the remaining studies included all grades of severity and did not perform any stratification.

As for the involved joints, most of the cited papers addressed a variety of affected joints in the same approach (knee, ankle, shoulder, wrist). A total of 7 papers focused on the knee (7,9,11,19,20,22,23) and 3 papers on the ankle (13,18,24).

3. Corticosteroids

Intra-articular administration of CS has a long record in the literature. A total of 4 papers (109 joints) dating back from 1988 were found.

A small pilot study on 10 patients (19 joints: Knee, elbow, shoulder, ankle, wrist) recommended to obey at least one of the following indications for intra-articular methylprednisolone: Chronic synovitis of at least 2 months' duration (heat, swelling, tenderness), recurrent hemarthrosis not responding (coagulation factor replacement, rest, physiotherapy) or advanced arthropathy without any signs of active inflammation. Short-term results (24 h, 4 and 8 weeks) indicated a clinically significant subjective improvement, reduction of the number of hemarthroses and of the amount of necessary clotting factor at all time-points of the study. The authors underlined the value of CS in the short-term, for early stages (prevention of progression) as well as for advanced stages (6). Another small prospective study on 10 knees with chronic synovitis with intra-articular methylprednisolone followed imagistic evolution (X-ray and ultrasound) at one year. They found excellent and good evolution for 7 out of 10 knees, fair for 2 out of 10 and poor for one knee. There was no information on joint severity (7).

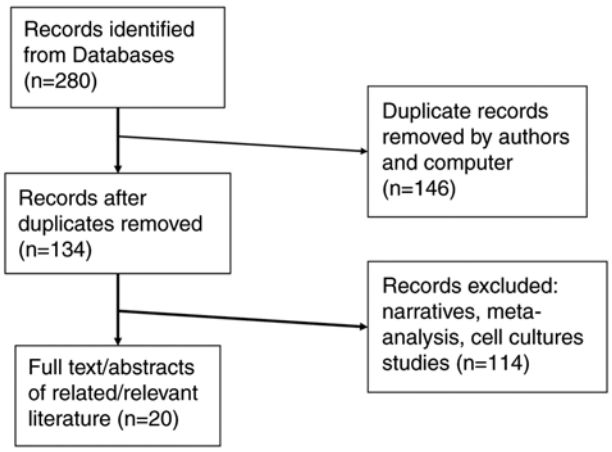

Figure 1. Selection process of records from databases.

A retrospective study on 34 patients (35 joints: Knee, ankle, shoulder) with severe advanced chronic synovitis (grades III and IV) received intra-articular dexamethasone (a combination of short- and long-acting forms).

Subjective and objective outcomes were good (54 and 63%, respectively), fair (34 and 26%, respectively) and poor (both 11%) after an average follow-up period of 1,5 years (8).

One comprehensive study (a retrospective and a prospective arm) included 45 joints (ankles, knees, elbows; various grades of severity) to receive intra-articular triamcinolone under ultrasound guidance. The indications were as follows: Unresponsiveness, inability, unwillingness or contraindication to alternative treatment strategies such as physical therapy, oral pain or anti-inflammatory agents. Pain relief was achieved within 48 h after injection, persisted at least 4 weeks and in certain patients 4 months. Ultrasound scan demonstrated resolution of hypervascularity within 1-4 weeks. A low Pettersson score (between 4 and 8) and haemophilia type B were associated with a longer pain relief period (14).

4. Hyaluronic acid

Of the 7 papers dealing with HA injection, six studies used low-molecular-weight HA (LMWHA) and one high-molecular-weight HA (HMWHA). Only two studies used stratification according to joint severity (1,10).

The first published prospective study from 2020 on 20 patients (21 knees) with 5 weekly injections of LMWHA reported improvement in the clinical and functional scores at 3 months (15 out of 21 knees), persisting at 24 months in 10 out of 21 knees. Failure of pain relief at 3 months was noted in 6 out of 21 knees and arthroscopic debridement was performed in 2 patients after 14 and 15 months. It is important to note that there was no initial severity assessment or stratification of joint arthropathy (9).

Intra-articular injection of elbows, knees and ankles (77 joints) with different LMWHA preparations, according to specific protocols (3-5 weekly doses/cycle, at least 2 yearly cycles) offered pain relief and functional improvement in the short-term and persistence of the benefits in the long-term, but at a lower level. With 60% of patients with severe joint involvement, the paper mentioned that there was a need for further therapies (drugs, physiotherapy) after the first cycle in 2 out of 18 elbows and in 10 out of 32 ankles. In the long-term (2-4 years), 6 out of 30 knees required surgery. The authors stated that the need for surgery was delayed (10). The same study group published another paper on chronic knee arthropathy and concluded that, in the short-term, all parameters improved, with the best evolution of pain relief, function (World Federation Haemophilia score) and quality of life (Short Form-36 questionnaire). In the long-term, there was a small decline in all items, with better values compared to pre-treatment and best evolution of functional aspects (Western Ontario and McMaster Universities arthritis index and range of motion). No joint severity stratification was performed (11).

A single intra-articular injection of LMWHA into the ankle (16 joints) under ultrasound guidance was reported to reduce pain to a certain extent in 78% of cases and this was statistically significant in 56% of cases at 3 months, persisting at 6 months. No stratification of joint severity arthropathy was provided (18). Another pilot study on 26 ankles (24 patients) to receive two intra-articular LMWHA injections 6 months apart reported pain relief and functional improvement over 1 year. Quality of life remained unchanged (24).

A small prospective study on symptomatic mild-to-moderate arthropathy of knee and ankles indicated that LMWHA (specific protocols: 3 monthly injections for knee, 2 monthly injections for ankle) offered clinically significant pain and functional improvement and reduction of the bleeding rate at one year. Ultrasound evaluation of the synovial status and joint effusion confirmed the clinical evolution. The authors concluded that early stages of arthropathy were successfully treated with LMWHA (21).

For severe chronic arthropathy (grade III) of ankles, knees, hips, shoulders and elbows, 3 weekly injections of HMWHA offered pain relief and functional improvement at one month, with a variable period of monitoring (up to 10 years, average 10,5 months). No X-ray modification was noted. 10,3% of joints failed to improve, mainly due to the high degree of joint involvement (1).

5. Platelet-rich plasma

A total of 3 papers reported on intra-articular administration of PRP. In a small case series (6 patients, 8 ankles) an intra-articular injection of 3-5 ml PRP was followed by clinically significant pain reduction, functional improvement (not significant) and, in 3 out 8 joints, mild synovial hypertrophy regression at 2 months (13). A prospective study on 28 joints (ankle, elbow, knee) that received 3-7 ml PRP (according to joint size) found significant pain and functional improvement, reduction of number of bleeding events and reduction in thickness of the synovium (according to MRI) at 3 and 6 months (16). Neither of the papers reported any complications, suggesting that the procedure was safe.

One single prospective, parallel-group, double-blinded, placebo-controlled, randomized clinical trial included 190 patients (190 knees) to receive three weekly PRP injections vs. three saline injections and found that, at 24 months, there was no difference in terms of clinical, functional and quality of life parameters (22).

Table I. Studies selected for analysis and their main characteristics.

First author, year	Features	No. of patients/joints	Protocol	Timing of evaluation	Evaluation methods/ parameters	Outcome	Comments	(Refs.)
Shupak, 1988	Pilot study, prospective, non-randomized, non-controlled	10 patients, 19 joints (10 knees, 4 elbows, 3 shoulders, 1 ankle, 1 wrist), all grades of severity	CS (methylprednisolone) 80 mg/knee 40 mg/other joints	24 h 4 weeks 8 weeks	Subjective improvement, Frequency of bleeds, Radiological staging, Synovial fluid analysis	24 h: 79% improvement; 8 weeks: 58% continued subjective improvement; 8 weeks: Reduced number of hemarthroses (from 7.7 to 1.9) and of amount of clotting factor (from 7616 to 2315 units)		(6)
Rodríguez-Merchán, 1994	Prospective	10 patients; 10 knees	CS (methylprednisolone)	1 year	X-ray; Ultrasound	4/10 excellent; 3/10 good; 2/10 fair; 1/10 poor	Lack of joint severity stratification	(7)
Fernández-Palazzi, 1997	Retrospective, non-controlled, non-randomized	34 patients; 35 joints (31 knees, 2 ankles, 2 shoulders); Grades III and IV	CS (dexamethasone, short- and long-acting combination)	1,5 years mean (1-2 years)	Subjective; Objective (clinical-pain, ROM, joint thickness; function-ability to perform ADL)	Subjective/ objective results: Good: 54/63%; Fair: 34/26%; Poor: 11/11%		(8)
Wallny, 2000	Prospective, non-controlled, non-randomized	20 patients; 21 knees	LMWHA (Hyalart 20 mg) x 5 weekly	3 months; 24 months	Clinical (pain VAS, WFH); Function (Aichroth score for knee); Imagistic (X-ray Pettersson score)	3 months: Improvement of clinical and functional parameters: 15 out of 21 knees. 24 months: Improvement persisted in 10 knees	Lack of joint severity strati-fication For 6 out of 21 knees, no pain improvement was reported at 3 months. 2 patients required arthroscopical debridement 14 and 15 months later	(9)

Table I. Continued.

First author, year	Features	No. of patients/joints	Protocol	Timing of evaluation	Evaluation methods/ parameters	Outcome	Comments	(Refs.)
Fernández-Palazzi, 2002	Prospective,non-randomized, non-controlled	25 (23 type A; 2 type B haemophilia); 29 joints (17 knees, 6 shoulders, 4 ankles, one elbow, one hip); Grade III arthropathies	HMWHA 3 weekly injections (Synvisc)	One month; Maximum 10 years; Average 10,5 months	Clinical (pain VAS, mobility-ROM, use of joint); Joint diameter; Imagistic (X-ray)	Pain relief; Increase in mobility; Increase n use of the joint; No alteration of X-ray	Great variability of follow-up intervals. No improvement in 10,3%	(1)
Carulli, 2012	Prospective, non-randomized, non-controlled	46 patients (77 joints, 14 elbows, 30 knees, 32 ankles); 60% with severe arthropathy	LMWHA (Orthovisc, Hyalgan, Hyalubrix) 3-5 weekly injections/cycle, at least 2 yearly cycles	6, 12 months, then yearly (average 6,3 years, 2-11 years)	Clinical (pain VAS); Imagistic (X-ray, Pettersson score); Functional (ROM, WFH, SF-36)	Short-term: Pain relief, functional improvement; Long-term: Regression of the effect, particularly function	Elbow: After the first cycle 2/18 needed further treatments (drugs, physiotherapy); Knee: Long-term 6/30 needed surgery (2-4years) Ankle: Short-term 10/32 needed further treatments (drugs, physiotherapy)	(10)
Carulli, 2013	Case series, prospective	27 patients (23 type A; 4 type B haemophilia); 27 knees	LMWHA yearly. 2003-2006: Hyalganx 5/2-week interval; 2007-2010: Hyalubrix x 3/4-week interval, 2-4 cycles	Short-term: 6 and 12 months Long-term yearly; Following period: 6,7 years (2-8)	Clinical (pain VAS, WFH); Imagistic (X-rays Pettersson score) Function (WOMAC) Quality of life (SF-36)	Short-term: All items, best on WFH, VAS, SF 36; Long-term Small decline, better than pre-treat, best on WOMAC and ROM flexion)	Lack of joint severity stratification. 5 patients required total arthroplasty in a 2-4 year interval after the last administration	(11)
Zelada, 2013	Prospective, non-randomized, non-controlled	4 patients, 27 joints (14 knees, 9 ankles, 4 elbows); severity	Intra-articular lavage (saline), LMWHA + triamcinolone +	1 and 3 months	Clinical (pain VAS); Function (WOMAC); Quality of life	Improvement of all parameters at one month and persistence at 3	No stratification according to joint severity	(12)

Table I. Continued.

First author, year	Features	No. of patients/joints	Protocol	Timing of evaluation	Evaluation methods/ parameters	Outcome	Comments	(Refs.)
	2-4 (Kelgreen Lawrence)		ropivacaine		(SF-36)	months; 10 out of 14 patients were satisfied at 3 months		
Teyssler, 2014	Case series, prospective	6 patients (6 ankles); Haemophilia type A; chronic synovitis	PRP, 3-5 ml	2 months	Clinical (pain, VAS); Functional (HJHS); MRI	Clinically significant improvement (pain); HJHS improvement, not significant; MRI: Mild synovial hypertrophy regression (3 out of 8 joints)	Joint severity varied from mild to severe	(13)
Martin, 2017	(Retrospective and prospective arms),Non-randomized, non-controlled	25 patients, 45 joints (14 ankles, 18 knees, 13 elbows); type A and B haemophilia; different grades of severity	40 mg CS (triamcinolone acetonide) + lidocaine 1%, repeated at least 3 months apart	4; 8; 12; 16 weeks	Clinical (pain, VAS, HJHS); X-ray (Pettersson score); Ultrasound exam (greyscale and color Doppler)	Pain relief in the first 48 h, up to 4-8 weeks; Reduced hypervascularity within 1-4 weeks	A low Pettersson score and type B haemophilia were associated with a longer pain relief period	(14)
Rezende, 2017	Case series, prospective, non-randomized, non-controlled	14 patients, 40 joints (knee, ankle, elbow, shoulder); Severe arthropathy	Saline solution lavage, followed by HA and triamcinolone injection	1, 3, 6 and 12 months	Functional tests (balance, speed); Bleeding events	Functional improvement (symmetry,speed); Reduction of bleeding events at 1 year	2 knees required joint replacement after one year	(15)
Caviglia, 2017	Prospective,non-randomized, non-controlled	19 patients (17 type A; 1 type B haemophilia); 28 joints (2 ankle, 7 elbow, 19 knee)	PRP, 3-7 ml according to joint size	3 and 6 months	Clinical (pain VAS, ROM);Function (HJHS); MRI (synovial thickening); Number of bleeding episodes	Decrease in joint bleeding episodes; Pain relief; ROM improved (not significant for flexion); MRI: Reduction in thickness of the synovium	Lack of severity stratification of arthropathy	(16)

Table I. Continued.

First author, year	Features	No. of patients/joints	Protocol	Timing of evaluation	Evaluation methods/ parameters	Outcome	Comments	(Refs.)
Patel, 2018	Retrospective, non-controlled (poster presentation)	10 patients (2 knees, 12 ankles); moderate and severe arthropathy	CS (7 joints); CS + HA (7 joints)	1 year	Clinical (pain VAS, HJHS); Bleeding rate; Functional (HAL)	Both groups improved (pain, function); Bleeding rate unchanged; CS + HA achieved a significantly better result than CS alone	4 patients from CS group required one more CS injection within a year	(17)
Poursac, 2018	Prospective, non-controlled, non-randomized	14 patients (16 ankles)	LMWHA single injection (Hyalgan 20 mg/ 2 ml) under ultrasound guidance	3 and 6 months	Clinical (pain VAS); Function (AOFAS ankle score, WFH); Imagistic (X-ray Pettersson)	Pain relief in 78% patients at 3 months; Significant pain relief in 56% at 3 months, sustainable at 6 months	Lack of joint severity stratification	(18)
Li, 2019	Prospective, non-randomized, open-label trial	22 patients (22 knees), haemophilia type A (n=20), haemophilia type B (n=2)	PRP, 2 ml (11 knees); HA, 2,5 ml, 5 weekly injections (11 knees)	1, 2, 3 and 6 months	Clinical (pain VAS, ROM); Functional WOMAC; SF-36; Ultrasound (hyperemia score)	Both were effective at 6 months; PRP showed better results on pain, ROM, WOMAC, ultrasound exam; SF-36 was similar		(19)
Liou, 2021	Case series, randomized, non-controlled	5 patients (5 knees) haemophilia type A	Course 1: LMWHA, PRP or LMWHA + PRP; Course 2: LMWHA + PRP (LMWHA Hya-Joint 2,5 ml; PRP 2,5 ml)	Monthly, up to 1,5 years	Clinical (pain VAS, HJHS) X-ray every 3 months (Pettersson score)	Improvement of pain and HJHS for all regimens	Too small a sample Discussion about the volume of injectate	(20)

Table I. Continued.

First author, year	Features	No. of patients/joints	Protocol	Timing of evaluation	Evaluation methods/ parameters	Outcome	Comments	(Refs.)
Carulli, 2020	Prospective, non-randomized, non-controlled	14 patients, 21 joints (ankles and knees), mild-to-moderate severity	LMWHA (Sinovial Forte), 3 monthly injections/knee, 2 monthly injections/ankle	1 year, then every 6 months (median, 20 months)	Clinical (pain VAS, ROM); X-ray (Pettersson); Ultrasound (synovial status, effusion); Functional (HJHS); Annual bleeding rate	Pain, HJHS, annual bleeding rate improved significantly at 1 year; ROM improved, not statistically significant		(21)
Duan, 2022	Prospective, randomized, parallel group, placebo-controlled, double-blinded	190 patients, 190 patients,	Group I: Three weekly PRP injections; Group II: Three weekly saline injections	Up to 24 months	Clinical (pain VAS, HJHS); Functional (WOMAC); SF-36; MRI	No difference between groups at all time-points for any parameter		(22)
Landro, 2021	Prospective, non-randomized, parallel	21 patients with bilateral knee involvement	Right knee: PRP; Left knee: PRP + LMWHA	3 and 6 months	Clinical (pain VAS); Functional (HJHS); Bleeding episodes; Subjective evaluation	Both knees noted pain relief and improved function at 3 and 6 months, no difference between left and right knee; Subjective improvement in left knee		(23)
Taylor, 2022	Pilot study, non-randomized, non-controlled	24 patients, 26 ankles	LMWHA (Ostenil Plus), 2 injections 6 months apart	Every 3 months for 1 year	Clinical (pain VAS); Functional (HJHS); Quality of life EQ-5D-5L	Significant pain relief and functional improvement at all time-points; No change in EQ-5D-5L	Lack of joint severity stratification	(24)

CS, corticosteroid; VAS, visual analogue scale; WFH, World Federation of Hemophilia score; SF-36, Short Form 36; LMWHA, low-molecular weight hyaluronic acid; HMWHA, high-molecular weight hyaluronic acid; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities arthritis index; ROM, range of motion; HJHS, hemophilia joint health score; ADL, activities of daily living; AOFAS, American Orthopedic Foot and Ankle Society; HAL, haemophilia activities list.

6. Comparative studies and combination strategies

A comparative prospective non-randomized study on 22 knees receiving either PRP or HA indicated that both therapies were effective at 6 months, with better results for PRP in terms of pain, function and ultrasound imaging (synovial hypertrophy) and a similar evolution of quality of life (19).

In order to increase the clinical benefits of intra-articular therapies, researchers combined CS (accredited with short-time effects) and HA (presumed to have a long-term effect). A small retrospective study on 14 joints (knee, ankle) comparatively observed the effect of CS vs. CS and HA administration on moderate to severe arthropathy. At one year, both strategies offered pain and functional improvement, with a significantly better evolution for the combination of CS and HA. A total of 4 out of 7 joints treated with CCS required a second injection within a year (17).

Another study suggested that the effect of viscosupplementation was able to be improved by joint lavage and the addition of CS. The rationale for lavage was to remove the intra-articular debris and factors causing inflammation. CS are known to improve the results of lavage and HA injection in osteoarthritis (25). A prospective study on 14 patients (27 joints: Knee, ankle, elbow) with different grades of severity (II-IV Arnold-Hilgartner) to receive lavage with saline solution followed by HA and CS administration improved clinical, functional and quality of life parameters at 1 month. The changes were obvious at 3 months with a relatively low level of statistical significance (12). A case series of 40 joints (knee, ankle, elbow and shoulder) with severe arthropathy (Arnold-Hilgartner stages III to V) were subjected to the same technique. At all time-points of observation of the study (1, 3, 6 and 12 months), there was significant functional improvement (balance, speed, activities of daily living) and reduction of the frequency of bleeding episodes. However, 2 knees required total replacement after one year due to persistent pain (15).

With the same purpose of augmenting the biological and clinical effects, the association between HA and PRP was tested in a case series study of 5 knees with chronic arthropathy with intra-articular courses. The first course consisted of one of the following: HA, PRP or HA plus PRP; the second course consisted of HA plus PRP. Up to 1,5 years, pain relief and functional improvement were noted for all knees, although only limited conclusions can be drawn on such a small sample. Certain practical issues arise concerning the mode of combining the two ingredients, as the concomitant administration may result in a large volume that is not anatomically normal to fill the joint space. The suggested procedure for the combined therapy was to administer 3 weekly injections of HA followed by PRP in the fourth week (20).

A prospective, non-randomized and parallel study on 21 patients with bilateral knee involvement compared one knee receiving PRP with the contralateral knee receiving PRP + HA. At 3 and 6 months, both knees improved significantly (pain relief, function, bleeding episodes and quality of life); there was no difference between them, while there was a subjective better evolution in the PRP + HA knees (23).

7. Conclusions

In the present review, 20 clinical studies were analyzed with a total number of 699 joints with chronic haemophilic arthropathy in different stages of severity, affecting different joints and receiving various intra-articular therapies, either unique agents or combinations. Most studies lack the double-blinded arm due to ethical considerations. The heterogeneity of the research prevents us from drawing clear-cut conclusions. However, certain features are to be underlined.

Numerous CS preparations are available for intra-articular use: Dexamethasone, betamethasone, triamcinolone, methylprednisolone and hydrocortisone. Triamcinolone (acetonide or hexacetonide) is preferred due to its decreased solubility and thus longer intra-articular duration of action. Numerous authors add lidocaine for numerous reasons: Lidocaine elicits immediate analgesic effects, which in turn aid in the confirmation of the correct injection site when ultrasound is not available; it also reduces the post-injection flare induced by precipitating CS crystals, as well as CS-associated soft tissue atrophy (26).

Intra-articular administration of CS has a relatively longer record of study, is safe and able to provide a short-term benefit in terms of pain relief and functional improvement, with the necessity to repeat the procedure within one year. Indications are all grades of severity of joint involvement, even in advanced stages or refractory cases.

There is an association between the Pettersson score and pain relief period following CS intra-articular injection (14). Pain-inducing inflammatory and angiopoietin changes in CS-responsive subjects may not prevail in early or late stages and the results of such treatment may be failure. In the early stages, pain may be induced by joint malalignment, and in the late stages by scarred tissue. Another interesting observation was that patients with haemophilia type B had a longer duration of pain relief than those with type A, consistent with previous studies. This may be explained by the fact that patients with haemophilia A have more frequent bleeding events and more severe forms of arthropathy than those with type B and the same amount of clotting factor deficiency (27).

Certain researchers have agreed that CS intra-articular injections are safe, while there is no formal consensus on the optimal frequency to repeat injections. There is a common practice to wait 3 months before re-injecting triamcinolone into the same joint. This may be a reasonable interval to assure at least 8 weeks of pain relief. Systemic absorption of a fraction of injected CS may occur, but it is presumed to be of limited significance, since the intra-articular dose is 40 mg triamcinolone, equivalent to 50 mg oral prednisolone (14). Triamcinolone (in the form of acetonide or hexacetonide) is preferred due to its decreased solubility and a longer intra-articular duration of action (28). Intra-articular dexamethasone may follow a course of 3 injections at 3-week intervals (29).

HA is a linear polysaccharide that constitutes the major part of the extracellular matrix of human articular cartilage. It is essential for the viscous-elastic and mechanical properties of synovial fluid, as it produces shock absorption, reduces pain and has anti-inflammatory and chondroprotective

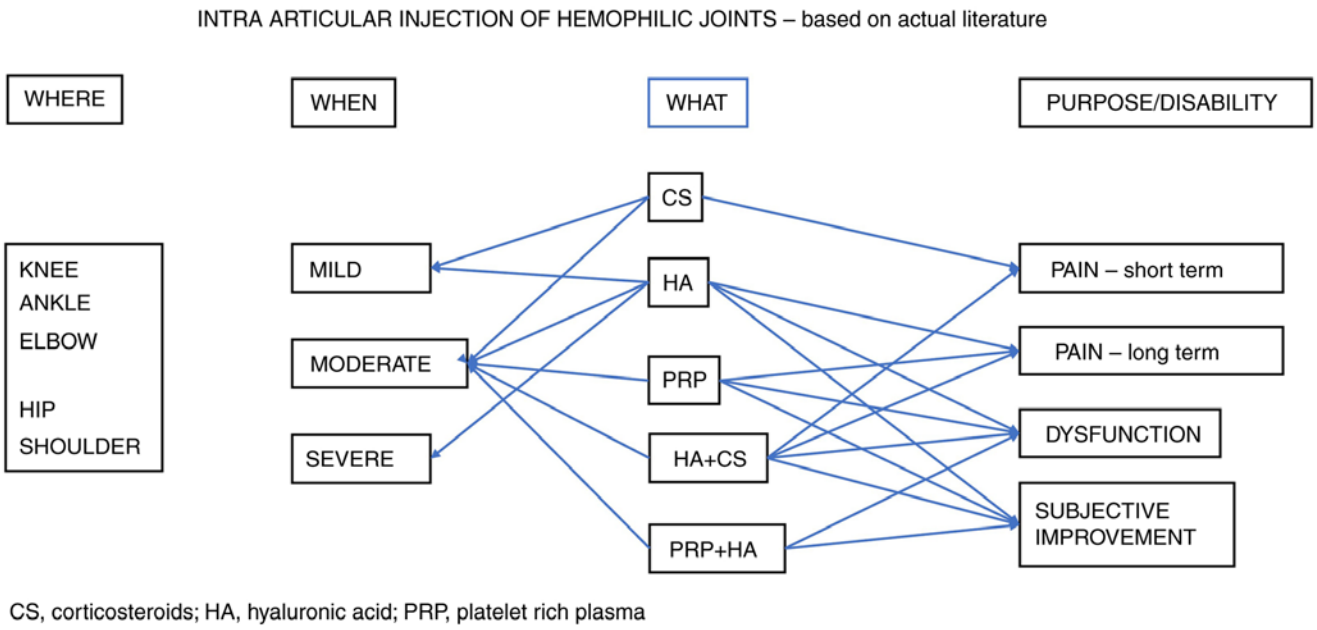

Figure 2. Summary of research on intra-articular injection of different medicines. CS, corticosteroids; HA, hyaluronic acid; PRP, platelet-rich plasma.

effects. The classification of HA preparations includes LMW (500-2,000 kiloDa) and HMW (6,000-7,000 kDa) agents. LMWHA achieves maximum concentrations in the joint and reduces inflammation but has a lower elastoviscosity than native HA. HMWHA agents result in a better increase in fluid retention into the joint and have a stronger anti-inflammatory effect (30). On the whole, HA significantly improved the clinical and functional status. One study indicated that early stages of arthropathy improved significantly (11) and another paper reported improvement of severe arthropathy, with a 10% failure rate (1). A low knee X-ray Pettersson score was associated with a better outcome after treatment (10).

In 2012, a review stated that, taking into account the papers published by then, potential haemophilic candidates for HA are young patients, with moderate pain and disability, with no severe deformities, who are unwilling to accept the risks of a surgical procedure (31). HA is accredited by numerous authors to postpone the time-point of surgical intervention (32).

The application of PRP in haemophilic arthropathy has raised the interest of researchers, as it contains various growth factors that promote chondrocyte proliferation and differentiation, stimulates synovial fibroblasts to synthetize HA, increases anti-inflammatory factors and decreases pro-inflammatory mediators (IL-1 and TNF-α) (33,34). In 2020, Caviglia *et al* (35) proposed, as an additional mechanism of PRP, the inhibition of the Fenton reaction. The Fenton reaction in the haemophilic joint consists of the oxidation of hemoglobin to methemoglobin and the generation of toxic hydroxyl radicals that induce chondrocyte death, alter the synthesis and stability of the cartilaginous matrix and promote synovial hyperplasia and inflammation.

A small number of studies reported on the use of PRP in haemophilic arthropathy. They ascertain that, in the short-term (1-2 months), there may be a clinically significant improvement, but in the long-term (24 months), there was no benefit.

Combining the above-mentioned agents may lead to better results. HA and CS, either as one injection or following joint lavage with saline, were used mainly for severe arthropathy. The lavage technique must be carried out under anesthesia in the operating room and the risk of infection is increased, as indicated by a study on osteoarthritic management (36). Intra-articular lavage with saline (washout) and CS administration was documented in cases of acute hemarthrosis in children, preventing the clinical evolution toward arthropathy. In fact, the joints of haemophilic boys who presented with acute hemarthrosis and received washout were followed over 11 years and found to be normal (37) (Fig. 2).

The combination of PRP and HA was used only for knee involvement in a small number of patients, with statistically comparable results to those of PRP alone.

The present study focused on intra-articular agents for chronic haemophilic arthropathy and concluded that there is a need for extensive studies on this subject, taking into account the various grades of joint involvement and different regimens of administration. Results should be provided for both short- and long-term outcomes, including clinical and functional aspects as well as subjective outcomes, including quality of life. There are ethical aspects that prevent the implementation of blinded or placebo-controlled arms of the studies, making the task more difficult.

The conservative approach cannot rely only on one modality, i.e., intra-articular agents, but on a complex management, adding oral drugs, physiotherapy and therapeutic exercise.

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Authors' contributions

DP and DC performed the literature search and selected the studies. MIS extracted the data from the studies. DP, DC, MIS analysed the data and wrote the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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