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REVIEW ARTICLE

Management of acute haemarthrosis in haemophilia A without inhibitors: literature review, European survey and recommendations

C. HERMANS,* P. DE MOERLOOSE,† K. FISCHER,‡ K. HOLSTEIN,§ R. KLAMROTH,¶ T. LAMBERT,** G. LAVIGNE-LISSALDE,†† R. PEREZ,‡‡ M. RICHARDS§§ and G. DOLAN¶¶ ON BEHALF OF THE EUROPEAN HAEMOPHILIA THERAPY STANDARDISATION BOARD

**Haemostasis-Thrombosis Unit, Division of Haematology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; †Unité d'Hémostase, Hôpitaux Universitaires de Genève, Geneva, Switzerland; ‡Van Creveld Clinic, Utrecht, Netherlands; §Onkologisches Zentrum, II. Medizinische Klinik und Poliklinik, Universitätsklinik, Hamburg, Germany; ¶Vivantes – Klinikum in Friedrichhain Klinik fuer Innere Medizin Haemophiliezentrum, Berlin, Germany; **CHU Kremlin – Bicètre, Paris, France; ††Laboratoire d'Hématologie, Groupe Hospitalo-Universitaire Caremeau, Nîmes, France; ‡‡Hospital Virgen del Rocio, Seville, Spain; §§Paediatric Haematology Department, Children's Day Hospital, St. James University Hospital, Leeds, UK; and ¶¶Queen's Medical Centre, University Hospital, Nottingham, UK*

Summary. Acute haemarthrosis is a frequent type of bleeding in individuals with haemophilia. Delayed and/or inadequate treatment can trigger a series of pathological changes within the joint, leading to a painful and disabling arthropathy. The early management of intra-articular bleeding has the potential to prevent chronic joint disease and may include a combination of factor replacement, rest, ice, rehabilitation and, in certain cases, joint aspiration. Little data are, however, available regarding the optimal management of acute haemarthrosis, especially with respect to replacement therapy and the use of adjunctive therapies (aspiration, avoidance of weight bearing and immobilization, as well as the use of anti-inflammatory medication and embolization). To provide more insight into the management of acute haemarthrosis in patients with haemophilia, a literature review was conducted. Concomitantly, current management was surveyed in 26 European haemophilia comprehensive care centres representing 15 different countries. The review highlights the need for future robust studies to better define the appropriate replacement therapy and the role of adjunctive therapies such as aspiration. The survey reveals much heterogeneity in the management of acute haemarthrosis across the EU. Within the constraints discussed, treatment recommendations are presented that reflect the literature, current practice and the clinical experience of the European Haemophilia Therapy Standardisation Board (EHTSB).

Keywords: haemarthrosis, haemophilia, recommendations, survey

Introduction

Acute haemarthrosis is one of the most frequent types of bleeding in individuals with haemophilia. Very young persons, not yet treated with prophylactic infusions of factor concentrate, and subjects treated on demand are at risk of developing acute haemarthrosis. In addition, although prophylactic treatment significantly reduces the incidence, it does not totally abolish the risk of acute haemarthrosis [1].

The key event in the development of haemophilic arthropathy is the extravasation of blood into the joint [2,3]. Although the precise mechanisms are still incompletely understood, *in vitro* and *in vivo* animal studies demonstrate that deposition of iron in the synovium causes a marked inflammatory response, which in turn leads to damage to cartilage. Iron initiates synovial cell proliferation, and it has been hypothesized that it may act through the induction of critical genes including *c-myc* and *mdm2* that control synovial cell proliferation and apoptosis respectively [4]. These synovial changes indirectly damage and destroy cartilage, but more

Correspondence: Cedric Hermans, MD, MRCP(UK), PhD, Haemostasis and Thrombosis Unit, Division of Haematology, Cliniques Universitaires Saint-Luc, Avenue Hippocrate, 10, 1200 Brussels, Belgium.
Tel.: +32-2-764-1740; fax: +32-2-764-8959;
e-mail: cedric.hermans@uclouvain.be

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recent data have shown that cartilage may be directly and independently affected by haemarthrosis. Biochemical markers of chondrocyte damage, such as impaired proteoglycan synthesis, may be seen after relatively short exposure to blood [3,5,6].

Inflammatory mediators such as IL-1α and TNF-α, released from monocytes/macrophages, are also important in synovitis and cartilage destruction, while recent experimental data demonstrate an apparent role for IL-10 in protecting joints from cytokine-mediated damage. Angiogenesis caused by VEGF release may also exacerbate synovitis [2,4]. Additionally, physical factors such as joint loading may act synergistically to cause long-term joint damage after joint bleeds [7]. *In vitro* studies demonstrate that these changes occur in a dose- and time-dependent manner, and that a duration of joint exposure to blood as short as 2 days may be sufficient to initiate long-term changes [5]. These issues may be important in guiding treatment for haemarthrosis.

Delayed and/or inadequate treatment of acute haemarthrosis can trigger a series of pathological changes within the joint, leading to painful and disabling arthropathy. The treatment of intra-articular bleeding conventionally involves a combination of factor replacement, rest, ice, rehabilitation and, in certain cases, joint aspiration. Few data are, however, available concerning the optimal management of acute haemarthrosis, especially with respect to the replacement therapy regimen, indications for aspiration, physiotherapy, and the use of anti-inflammatory agents [8].

For these reasons, an extensive literature review of the pathophysiology and the management of acute haemarthrosis in patients with haemophilia A and B was conducted, and a survey carried out to provide information on current practice in 26 European haemophilia centres representing 15 different countries. All survey participants were members of the European Haemophilia Therapy Standardisation Board (EHTSB), an established group of experienced haemophilia centre-based physicians responsible for treating a total of 3633 people with severe haemophilia [9].

The aim of this study was to review current data, to assess current practice and to identify areas of controversy, unresolved issues and topics for future research. Data accrued from the literature and the survey, as well as the clinical experience of the treaters, served as a platform for extensive discussions within the network of the EHTSB to develop consensus recommendations for management of acute haemarthrosis.

Materials and methods

Literature review

A review was performed of published evidence regarding the pathophysiology and management of acute haemarthrosis in patients with haemophilia A. The latter included: factor substitution therapy, imaging techniques, arthroscopy and adjunctive therapy (acute pain control, aspiration, physiotherapy, cooling measures, anti-inflammatory agents and angiographic embolization). Relevant papers were identified using both PubMed and Medline searches (from 1966 to January 2009) using as keywords h(a)emarthrosis, h(a)emophilia, treatment, therapeutics and pathophysiology. Search terms used and number of papers recovered are shown in Table 1. Existing guidelines on the management of acute haemarthrosis not referenced in PubMed were also collected and critically reviewed by members of the EHTSB.

Survey

Treatment and management practices were surveyed using questionnaires relating to three clinical cases designed to illustrate typical presentations of acute haemarthrosis in patients with haemophilia:

Case 1: An 8-year-old boy (30 kg) with severe haemophilia A without target joint, on primary prophylaxis since the age of 2 years [750 units recombinant factor VIII (rFVIII) three times a week], with major swelling of his left knee on a Sunday morning. He had injected himself on Friday and reported falling from his bicycle on Saturday afternoon.

Case 2: A 43-year-old man (80 kg) with severe haemophilia A and chronic arthropathy without active target joint, receiving on-demand home treatment, wakes up with major swelling of his left knee on a Sunday morning.

Case 3: An 8-year-old boy (30 kg) with severe haemophilia A without target joint, on primary prophylaxis since the age of 2 years (750 units rFVIII three times a week), with pain and slight limitation of movement of his left knee on a Sunday morning. He had injected himself on Friday with his standard prophylaxis treatment. He had been playing with friends.

Table 1. Literature search strategy.

1	Hemarthrosis or haemarthrosis	1931
2	(Haemophilia or haemophilia).mp [mp = title, original title, abstract, name of substance word, subject heading word]	17 877
3	1 AND 2	971
4	Treatment.mp or therapeutics	2 256 487
5	4 AND 5	382
6	Limit 5 to humans	377
7	Pathophysiology.mp.	57 955
8	7 AND 3	10

The 377 papers in '6' were searched manually to a short list of 159 papers, these and the 10 papers from '8' were reviewed by four members of the group to produce the final selection of 65 papers that formed the basis of this current paper. In addition, PubMed was searched using the same terms.

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Information was collected on target levels of clotting factors, duration of treatment, treatment modality (continuous infusion vs. bolus), monitoring of factor levels, screening for inhibitors, use of antifibrinolytics, non-weight bearing, immobilization, application of ice packs, physiotherapy assessment and physical therapy.

Results

Literature review

The number of papers located by the literature search is shown in Table 1. A short list of 169 papers was reviewed by the group and 65 papers were identified that formed the database for this current paper. Several guidelines were also included.

What can we learn from haemarthrosis in patients without haemophilia?

There is no published evidence that individuals without haemophilia or coagulopathy sustain chronic arthropathy following a single acute haemarthrosis caused by trauma, pseudoaneurysm or synovial tumour.

Haemarthrosis has been reported occasionally in patients receiving heparin, low-molecular weight heparin or thrombolytic agents, but most reports concern haemarthrosis in patients receiving vitamin-K antagonists. Long-term joint damage does not occur after a single episode of haemarthrosis in these patients, but arthropathy can occur following recurrent joint bleeds and is identical to that seen in haemophilia on X-ray and pathological examination. Recommended management includes rest, careful joint aspiration or temporary discontinuation of anticoagulation [10,11].

Factor substitution therapy

Very few studies have evaluated the impact of different factor replacement regimens on outcomes in haemarthrosis. There is no standardization of outcome measures and it is therefore difficult to compare current studies with earlier publications. A review [12] of 13 studies on the treatment of joint bleeds published between the late 1960s and early 1980s [13–25] found that most investigators recommended low initial doses of 10–20 IU kg^{-1} of factor concentrate or cryoprecipitate, with reported success as high as 75–100% of cases (Table 2) but were more often associated with a second treatment. More recent publications with recombinant clotting factor concentrate using 25–40 IU kg^{-1} $bleed^{-1}$ have reported success rates of up to 88% for a single treatment [26–29].

Current consensus guidelines on the management of acute haemarthosis (Table 3) recommend early infusion with clotting factor concentrates to achieve plasma levels of FVIII between 40% and 60%, or between 10% and 20% when there is resource constraint [12,30–39]. It is not known whether shoulder and hip bleeds require higher target levels for a longer duration.

If symptoms do not settle, or if the haemarthrosis is severe, guidelines recommend a second dose 12–24 h later. Although rarely performed, continuous infusion has also been used in this setting [30–32,34,37,39].

Table 2. Summary of reports describing outcome of single lower doses of factor replacement for acute haemarthrosis [Ref. (12)].

Year of publication	Study reference	Therapeutic material	No. haemarthroses	Dose FVIII/FIX (IU kg^{-1})	Success (%)
1967	13	Cryoprecipitate	25 (in 12 patients)	23	56–64
1969	14	FVIII concentrate	51 (in 14 patients)	20–30	92
1974	15	FVIII concentrate	51 (in 9 patients)	10	97
1975	16	FVIII concentrate	51 (in 9 patients)	10	96
1977	17	FVIII concentrate	62 (in 21 patients)	8–12	100
1977	18	FVIII concentrate	106	7–9	90
			173	11–13	79
			64	15–17	94
1977	19	FVIII concentrate	549 acute bleeding	7.5–12.5	89
			episodes (in 14 patients)	12.5–20	94
1978	20	FVIII/FIX concentrates	60 (in 37 patients)	3–7	100
1979	21	Cryoprecipitate	988*	31	99
1979	22	FVIII concentrate	99 (in 6 patients)	5–8	85
				3	71
1980	23	FVIII concentrate	142 knee, 118 elbow; 79 ankle	7	67
				14	95
				28	100
1981	24	FVIII concentrate	144 (elbow in 27 patients)	11–16	78
1982	25	FVIII concentrate	95 (in 42 patients)	7	89
			106 (in 42 patients) (ankle)	14	77

FVIII, factor VIII; FIX, factor IX.

*Success was calculated by plotting failure vs. dose of factor. A total of 988 episodes were studied but it is not possible to state how many were haemarthroses and what dose of factor was used for each.

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Table 3. Management of acute haemarthrosis in haemophilia: summary of published guidelines.

Author and Country	Reference	Replacement therapy	Physical therapy	Pain control
WFH (no resource constraint)	30	Peak FVIII 40–60%; duration: 2–3 days, sometimes longer if inadequate response	Physiotherapy	Immobilization, ice, analgesics
WFH (significant resource constraint)	30	Peak FVIII/FIX 10–20%; duration: repeat infusion 2–3 days	Physiotherapy	Immobilization, ice, analgesics
National Guidelines, New Zealand	31	Early single dose of FVIII 20 UI kg^{-1}; FIX 30 UI kg^{-1}. Second dose 12–24 h later	Maintain muscle function and strength	Immobilization, ice, analgesics
Gringeri; Santagostino *et al.*, Italy	32–33	Early single dose: FVIII 20 UI kg^{-1}; FIX 40 UI kg^{-1}; Second dose if necessary	Physiotherapy	Immobilization, ice
GREHCO (Groupe de Recherche et d'Etudes de l'Hémophilie du Centre et de l'Ouest France)	34	Early single dose FVIII 20–30 UI kg^{-1} – FIX 30–40 UI kg^{-1}. Constitutive haemarthrosis: FVIII 20–30 UI kg^{-1} 12 h^{-1}; FIX 30–40 UI kg^{-1} 24 h^{-1}	Physical therapy is helpful to restore full activity	Immobilization, ice
Germany Bunesärztekammer, Germany	35	FVIII 20–40 UI kg^{-1}. FIX 20–40 UI kg^{-1}. Duration unspecified	Unspecified	NR
Berntorp, Sweden	36	FVIII 20 UI kg^{-1}; FIX 40 UI kg^{-1}. Duration unspecified	Physiotherapy is needed to replace lost functions: programme straining after bleeding, work with methods that ease pains: pool training, massage, heat-cold, relaxation	Paracetamol forms, if necessary, combined with extropropoxifen or codeine
Mahlangu, South Africa	37	FVIII 25 UI kg^{-1}; FIX 30 UI kg^{-1}; FVIII level of 40–60% for minor bleeds, 80–100% for major bleeds once or twice daily until pain disappears	Rest affected joint/limb and immobilize with non-circumferential cast	Apply ice, 5 min on and 10 min off; analgesics; start rehabilitative exercises under factor cover as soon as symptoms disappear
Kasper, Georgia	38	FVIII 20 UI kg^{-1}; FIX 40 UI kg^{-1}. Duration unspecified	Physiotherapy	Ice, consultation if symptoms persist >3 days
Srivastava *et al.*, India	39	Factor replacement for severe bleeds to achieve a level of about 10%. One or two doses are given	Physiotherapy is initiated as soon as pain subsides	

FVIII, factor VIII; FIX, factor IX; NR, not recommended.

Acute pain control

There are few data addressing the treatment of acute pain in acute joint bleeds, as most studies focus on the treatment of chronic pain. A retrospective questionnaire study among persons with haemophilia with acute and chronic pain did not yield any useful information on the relative efficacy of analgesics used to treat acute haemarthrosis [40].

In principle, both opioid and non-opioid analgesics could be used to treat pain in acute haemarthrosis, but strong opioids are rarely used in practice. Among non-opioid analgesics, paracetamol (acetaminophen) has analgesic and antipyretic effects. It is generally recommended for mild and moderate pain, but it should be used with caution in patients with chronic liver disease [41]. Some national guidelines (Table 3) recommend that paracetamol may be combined with mild opioids such as codeine to enhance the analgesic effect.

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and diclofenac have been used with caution in acute haemarthrosis. There is a risk of platelet dysfunction and bleeding and gastrointestinal adverse effects because they inhibit both cyclo-oxygenases COX-1 and COX-2. Newer, selective COX-2 inhibitors such as etoricoxib and celecoxib have been shown to be effective and safe in haemophilia patients [42,43]. There is, however, little evidence to support their use in acute haemarthrosis apart from a small retrospective study, reporting that a median of 10 (5–14) days treatment with rofecoxib had no additive effects on outcomes or pain control [44].

A high incidence of cardiovascular events led to the withdrawal of rofecoxib by the manufacturer, but all COX-2 inhibitors are associated with increased cardiovascular risk in long-term use [45]. They should therefore be used with caution in patients with significant cardiovascular risk factors. Similar to traditional NSAIDs, COX-2 inhibitors may also cause renal toxicity, especially in older patients and those with impaired renal or hepatic function, or heart failure.

Steroids

Although treatment with intra-articular corticosteroid injection has been described for chronic synovitis associated with haemophilia, there is no literature addressing its use in acute haemarthrosis. Studies have

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evaluated the potential role of systemic corticosteroids in dampening the intra-articular inflammatory response after acute haemarthrosis [46–48]. Any benefits associated with treatment with oral corticosteroids are short-lived and, because of their frequent side-effects, their use is limited and not recommended by guidelines [48].

Other local measures. Iontophoresis is a non-invasive method of delivering electrically charged medication through the skin. Hyaluronic acid, a major constituent of connective tissue, can be delivered transdermally when it is hydrolysed by the positive-charged enzyme hyaluronidase [49]. A single study including 500 patients with haemophilia concluded that hyaluronidase iontophoresis was a useful adjunctive treatment of both haemarthrosis and haematomas [50]. Caution is, however, recommended until further studies demonstrate the safety of this technique, because hyaluronidase is indiscriminate in breaking down the intercellular ground substance matrix and may therefore damage cartilage by opening a path for infection and other toxins [51].

Rest and splinting. The World Federation of Haemophilia Guidelines for lower limb bleeding episodes recommend bed rest (1 day) followed by avoidance of weight-bearing and the use of crutches when ambulating, and elevation when sitting (3–4 days). For the knee, a compressive bandage is adequate, although in very painful cases the bandage should be supplemented with a long-leg posterior plaster splint. For the ankle, a short-leg posterior plaster splint is recommended. For the upper limb, usually a sling (for the shoulder) or a long-arm posterior plaster splint (for the elbow) will provide sufficient rest, support and protection. Lifting and carrying heavy items should be avoided until the bleeding has resolved (4–5 days) [52].

Arthroscopy

There is no literature supporting a role for arthroscopy in the acute management of haemarthrosis in haemophiliacs, and it is not recommended by current consensus guidelines. There is no consensus about the role of arthroscopy in patients with normal haemostasis presenting with haemarthrosis following trauma. Although arthroscopy may contribute to accurate diagnosis, it does not influence acute management in adults [53,54] or in children [53].

Aspiration/arthrocentesis

The technique of aspiration of an acute haemarthrosis in patients with haemophilia has been described since 1963 [55]. Protagonists of the procedure suggest that removal of blood may provide immediate pain relief and may lower the risk of haemophilic arthropathy by reducing the duration of synovial exposure to blood and iron. There is very limited literature addressing this area of management in patients with haemophilia, and, except for selected cases, it is not generally recommended in consensus guidelines.

A single randomized control trial included 22 adults with intermediate swelling of the knee joint, 11 of whom underwent aspiration under local anaesthesia and intravenous analgesia [56]. The knee was then bandaged, and neither splinting nor intra-articular steroid injection were used. At day 1, there was a statistically significant improved range of movement in patients who had undergone aspiration, but by day 5 there was no difference between the groups. Aspiration was painful in a subset of patients. The authors recommended that aspiration be used only for tense effusions, and may be offered to patients with intermediate effusions if they wish rapid resolution of symptoms, but that they should be warned of the risk of pain during the procedure.

In 1975, a retrospective study of 27 cases of children and adults with haemophilia and a knee haemarthrosis concluded that aspiration was safe and effective in restoring early joint function in established severe haemarthrosis [57]. The authors noted a gain of extension and an overall increase in range of motion by day 4. Patients who had undergone aspiration returned to normal school and employment within 48 h of the procedure, compared with an average of 3–7 days in-patient hospitalization for cast or traction immobilization in descriptive historical controls. There have been no recent studies of aspiration of haemophilic knee bleeds.

A case report found symptomatic improvement in all five patients who underwent ultrasound aspiration of hip haemarthrosis that failed to resolve on factor replacement. Factor VIII replacement was given to cover the aspiration, and the authors recommended aspiration of haemarthrosis in this group of patients [58].

Physiotherapy

Most consensus guidelines recommend physiotherapy following acute haemarthrosis in patients with haemophilia (Table 3). There is, however, no significant evidence to support recommendations for specific interventions. In 1964, Greg outlined the need for rest, elevation, application of an ice pack and immobilization of the joint by positioning on foam, rubber or light plaster of Paris shells [59]. Immobilization was recommended for no more than 5 days, and early active movement was advised to assist in the absorption of any residual blood. Skin traction to the lower leg was recommended if the ankle affliction was not too great. The paper advised very careful physiotherapy, initiated

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after the end of immobilization and including early quadriceps drill and resistance exercises. The final recommendation was to protect the knee joint for several weeks by crutch walking until the quadriceps muscle was strong enough to stabilize the joint.

Cooling measures

The application of ice is recommended by consensus guidelines (Table 4) but little is known regarding the safe periods of application, or the relative safety of cryotherapy devices such as the Cryo Cuff™ (DJO, Vista, CA, USA) when used in the home setting by patients suffering from severe haemophilia and related bleeding disorders. There is one observational study providing some evidence that cooling procedures provide symptomatic and possibly therapeutic benefit in treating haemarthrosis. In the study, 12 selected patients with severe haemophilia A or B or type 3 von Willebrand's disease (VWD, age 5–45 years) used Cryo Cuff™ as part of a PRICE (protection, rest, ice, compression and elevation) regimen [60]. The device was applied for 15 min, repeated every 1–2 h as tolerated. After 1 year's treatment, all patients agreed or strongly agreed that the device had a positive impact in reducing pain and 78% either agreed or strongly agreed that the device significantly reduced swelling associated with haemarthrosis. There was no conclusive evidence that the device reduced the amount of factor concentrate used to treat the acute bleeding episode, but no patient reported a subjective delay in achieving haemostasis or the need for extra factor replacement therapy as result of the use of the device. No other adverse effects were reported.

Imaging techniques

Current guidelines do not recommend imaging examination in acute haemarthrosis unless there are unusual features e.g. trauma or infection. Most studies have used imaging to assess the long-term consequences of repeated joint bleeds in haemophilia, but one study reviewed the results of routine ultrasound on admission in 47 acute bleeds (both soft-tissue bleeds and haemarthrosis) in 33 patients with haemophilia, and one patient with VWD. The authors concluded that ultrasound was useful in managing soft-tissue bleeds, but not in joint bleeds except for haemarthrosis in the hip joint [61]. There is no evidence that MRI is valuable in diagnosing acute haemophilic haemarthrosis (spontaneous or traumatic).

Angiographic embolization

Rapid onset of bleeding, resulting in complete loss of function and intense pain, occurs occasionally after joint replacement or spontaneously in haemophilic haemarthroses. If these bleeds are unresponsive to high dose treatment, investigation for vascular abnormalities should be undertaken and if present, angiographic embolization should be considered. Angiographic embolization with a non-adhesive, liquid embolic agent requires a skilled radiologist, but two recent studies suggest that it is a promising therapeutic option in this situation [63,64].

A group from Amsterdam has treated 23 cases of massive knee or elbow bleeding in 18 patients by

Table 4. European Survey of the Management of Acute Haemarthrosis.

	Case 1, 8-year	Case 2, 43-year	Case 3, 8-year
Reason for haemarthrosis	Post-trauma	Spontaneous	Spontaneous
Swelling	Major	Major	Moderate
Current replacement therapy	Prophylaxis	On-demand	Prophylaxis
Dosage on day 1 (%)			
30 U kg^{-1}	25	31	75
40 U kg^{-1}	35	54	19
50 U kg^{-1}	40	14	6
Replacement on day 2 (%)			
Yes	95	100	66
Replacement on day 3 (%)			
Yes	77	90	22
Replacement on day 4 (%)			
Yes	54	40	27
Infusion(s) day^{-1} (%)			
1 day^{-1}	19	24	88
2 day^{-1}	81	76	12
Continuous infusion (%)			
Yes	0	4	0
No	100	96	100
Inhibitor screen on admission (%)			
Yes	28	15	29
No	72	85	71
Radiological examination (%)			
Yes	57	27	22
No	43	73	77
X-ray (%)			
Yes	50	18	5
Ultra-sound (%)			
Yes	13	13	16
MRI (%)			
Yes	0	4	0
Aspiration (%)			
Yes	19	28	0
No	81	72	100
Immobilization (cast) (%)			
Yes	71	63	38
No	29	37	62
Non-weight bearing (%)			
Yes	85	85	44
No	15	15	56
Physiotherapy (follow-up) (%)			
Yes	44	44	37
No	56	56	63
Drugs (%)			
Oral steroids	0	0	10
NSAIDs	27	45	5
Analgesics	86	86	47
Tranexamic acid	18	13	10
Ice (%)			
Yes	95	100	89
No	4	0	11

NSAID, non-steroidal anti-inflammatory drug.

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selective arterial catheterization using a micro catheter when an excessive blush, suggesting hyperaemic tissue or ruptured microaneurism, was found on angiography [62]. Embolization was effective in 20 of 23 patients, but rebleeding occurred in seven patients. Repeat embolization resulted in complete control in five and reduced bleeding in two of these patients. Complications occurred in six of the 31 procedures: three patients experienced pain in the affected joint, one a temporary spasm of the artery, one a small thrombus of the artery and one a psoas bleed.

A second study recently reported the beneficial effect of embolization in seven patients with severe haemophilia A or haemophilia B experiencing recurrent massive bleeds of one elbow or knee joint in the absence of trauma and despite intensive secondary prophylaxis [63]. Following angiographic identification and embolization of the bleeding arteries in eight joints (six elbows and two knees), there were no recurrent severe bleeds unresponsive to coagulation factor replacement during a mean of 16 months follow-up. The consumption of factor concentrate decreased to one-third of the amount consumed before embolization.

Assessment of outcome. As recently emphasized, patient reports of efficacy of treatment of haemophilia-related joint bleeding are by definition subjective, yet are often the primary outcome in studies comparing therapies [64]. Verbal descriptors such as effective, partially effective, poorly effective, not effective are treated as dichotomous or categorical variables in analyses, lowering the statistical power relative to that which might be achieved with a continuous variable. Pain recording on a 100-mm visual analogue scale (VAS) during the course of joint bleeding was recently found to have more power than a dichotomous variable and when used with verbal descriptions of efficacy to improve the overall accuracy of assessment [64].

Survey

As shown in Table 4, for moderate haemarthrosis, a first dose of 30 U kg^{-1} FVIII was given by 75% of treaters once a day (88%) and repeated on day 2 (66%) and up to day 4 (27%). At presentation of a severe haemarthrosis, a first dose of 40–50 U kg^{-1} FVIII was given by 68–75% of treaters and repeated on day 1 (76–81%). Replacement therapy was continued up to day 3 (77–90%) or 4 (40–54%).

The following investigations were advised: inhibitor screen by 15–27% of the respondents; factor assays by 70%; and radiological examination by 22–57% of the cases. Aspiration was considered by 19–28% of the physicians in major haemarthrosis only.

Active interventions were recommended as follows: physiotherapy by 37–44%of the respondents; immobilization (splint or cast) by 38–71% and non-weight-bearing by 44–85%. Analgesics were used by most physicians (47–86%), but corticosteroids, NSAIDs and antifibrinolytic agents were used infrequently (usually <20%).

Discussion

Despite the tremendous benefit offered by primary prophylaxis, haemarthrosis remains an important clinical problem for individuals with haemophilia A and B, and may lead to chronic synovitis and haemophilic arthropathy. No comprehensive review of the management of acute haemarthrosis in patients with haemophilia has been published recently. This paper provides a comprehensive literature review of published data as well as a survey of current practice among a large group of European haemophilia treaters.

Interesting conclusions can be drawn from the literature review. Although replacement therapy represents the first step in the management of acute haemarthrosis, very few randomized controlled trials have evaluated the appropriate levels of FVIII or FIX and the optimal duration of treatment. Relatively low doses, ranging from 3 to 30 IU kg^{-1} of factor, derived from studies published between 1967 and 1982 were reported to be successful. The criteria for success were not well defined in these studies and make comparison with later, more stringent, studies difficult. More recent studies of recombinant clotting factor concentrates using much higher doses (25–40 IU kg^{-1} $bleed^{-1}$) and employing better defined outcome criteria report success of up to 88% with a single infusion. In the past, variation in the literature has been reflected in the inconsistency in published guidelines. Our survey reveals a consistent approach in line with the more recent studies. There are few published data on the optimal management of less common joint bleeds such as hips and shoulders.

As illustrated by the literature review, there is little evidence-based information to determine the role of diagnostic procedures (radiological examination, arthroscopy) or adjunctive therapies (aspiration, pain control, physiotherapy, cooling measures, anti-inflammatory agents and embolization) in the management of acute haemarthrosis and our survey shows significant heterogeneity in approach. This lack of evidence is again well reflected in current guidelines, which do not provide standardized and detailed protocols of adjunctive therapies. Such information appears, however, critical in view of recent insights into the pathophysiology of haemophilic arthropathy and the understanding of the blood toxicity. Although non-weight bearing appears to be an important adjunctive measure in all patients, the role of joint aspiration to preserve joint function in patients with major haemarthrosis remains to be clarified.

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This survey, conducted among a large group of treaters caring for several thousand haemophilia patients, provides interesting information on treatment practices, including target factor levels, duration of treatment and use of certain treatment modalities. The survey highlights much heterogeneity in the management of acute haemarthrosis across the EU. The prescribed treatment regimens were usually more intensive, targeting higher factor levels, than those reported in the literature and current guidelines. Only a minority of the treaters considered joint aspiration to be a useful adjunctive treatment.

Treatment recommendations

Because of the limitations of the literature, it is not possible to provide evidence-based guidelines for the optimal management of acute haemarthrosis in patients with haemophilia. However, based on the results of literature review, survey and discussion within the EHTSB, consensus was reached on the following recommendations [the level of evidence (see Table 5) is shown in parenthesis]:

Replacement therapy. Recent studies and clinical consensus quote and support initial treatment with 25–40 IU kg^{-1} FVIII concentrate. In the vast majority of cases, this will resolve with one treatment [26–29]. Higher doses such as 50 IU kg^{-1} may be necessary for more severe bleeds e.g. post-traumatic. Replacement therapy should be initiated as soon as possible and repeated until satisfactory resolution defined as resolution of pain and recovery of function (grade B, level III).

Acute analgesia and anti-inflammatory agents. Immobilization and the use of ice may be helpful in the relief of pain and to resolve the bleed. There are no clear studies to guide choice of analgesia, but based on its efficacy and side-effect profile we recommend paracetamol for mild to moderate pain, with caution in patients with liver disease. Opiates may be necessary for severe pain. We recommend short-term treatment with selective COX-2 inhibitors in preference to non-selective NSAIDs where available (grade C, level IV).

There is no literature to support the treatment of acute haemarthrosis with intra-articular or systemic corticosteroids in patients with haemophilia. We do not recommend the use of corticosteroids (grade C, level IV).

Radiological evaluation. We do not recommend the routine use of imaging in the management in acute haemarthrosis. There is some evidence that ultrasound may be useful in the assessment of suspected haemarthrosis of the hip. Imaging should be reserved for patients presenting with atypical features, major swelling or trauma of a joint to exclude a concomitant traumatic lesion (grade C, level IV).

Aspiration. Aspiration may be appropriate to provide early symptomatic relief of a tense haemarthrosis. An experienced professional, using aseptic techniques, should perform the procedure only after adequate clotting factor concentrate replacement. The long-term benefits of joint aspiration remain to be determined (grade C, level IV).

Arthroscopy. Given the uncertainty in patients with normal haemostasis, and the absence of studies in bleeding disorders, we do not recommend arthroscopy in routine management of patients with acute haemarthrosis associated with haemophilia (grade C, level IV).

Angiographic embolization. Angiographic embolization may be considered in recurrent joint bleeds caused by vascular abnormality. In the light of limited clinical experience to date, we recommend that the procedure should only be undertaken at experienced centres (grade C, level IV).

Physical therapy. There is no significant evidence base to support recommendations for specific physical therapy interventions. Cooling measures reduce pain and swelling. We recommend immobilization and non-weight bearing for most patients, followed by rehabilitative physiotherapy under factor cover (grade C, level IV).

In conclusion, this study provides both a comprehensive review of the available literature and a large survey of the management of acute haemarthrosis in patients with haemophilia. This review highlights the need for robust future studies to better define the appropriate replacement therapy and the role of adjunctive therapies such as aspiration. Local practice and national

Table 5. Grading of recommendations and levels of evidence.

Grade	Level	Type of evidence
A	Ia	Evidence obtained from meta-analysis of randomized studies.
A	Ib	Evidence obtained from at least one randomized controlled trial.
B	IIa	Evidence obtained from at least one well-designed controlled study without randomization.
B	IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
B	III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies.
C	IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

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guidelines may need to be revised in light of recent advances in the understanding of the pathogenesis of haemophilic arthropathy. Within the constraints discussed, treatment recommendations are provided that reflect the literature, current practice and the clinical experience of the EHTSB.

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References

1 Manco-Johnson MJ, Abshire TC, Shapiro AD *et al.* Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **6**: 535–44.
2 Lafeber FP, Miossec P, Valentino LA. Physiopathology of haemophilic arthropathy. *Haemophilia* 2008; **14**(Suppl. 4): 3–9.
3 Roosendaal G, Jansen NW, Schutgens R, Lafeber FP. Haemophilic arthropathy: the importance of the earliest haemarthroses and consequences for treatment. *Haemophilia* 2008; **14**(Suppl. 6): 4–10.
4 Valentino LA, Hakobyan N, Enockson C. Blood-induced joint disease: the confluence of dysregulated oncogenes, inflammatory signals, and angiogenic cues. *Semin Hematol* 2008; **45**(2 Suppl. 1): S50–7.
5 Jansen NW, Roosendaal G, Bijlsma JW, DeGroot J, Lafeber FP. Exposure of human cartilage tissue to low concentrations of blood for a short period of time leads to prolonged cartilage damage: an *in vitro* study. *Arthritis Rheum* 2007; **56**: 199–207.
6 Jansen NW, Roosendaal G, Bijlsma JW, DeGroot J, Theobald M, Lafeber FP. Degenerated and healthy cartilage are equally vulnerable to blood-induced damage. *Ann Rheum Dis* 2008; **67**: 1468–73.
7 Hooiveld MJ, Roosendaal G, Jacobs KM *et al.* Initiation of degenerative joint damage by experimental bleeding combined with loading of the joint: a possible mechanism of hemophilic arthropathy. *Arthritis Rheum* 2004; **50**: 2024–31.
8 Ribbans WJ, Giangrande P, Beeton K. Conservative treatment of hemarthrosis for prevention of hemophilic synovitis. *Clin Orthop Relat Res* 1997; **343**: 12–8.
9 Astermark J, Morado M, Rocino A *et al.* Current European practice in immune tolerance induction therapy in patients with haemophilia and inhibitors. *Haemophilia* 2006; **12**: 363–71.
10 Palareti G, Leali N, Coccheri S *et al.* Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet* 1996; **348**: 423–8.
11 Thumboo J, O'Duffy JD. A prospective study of the safety of joint and soft tissue aspirations and injections in patients taking warfarin sodium. *Arthritis Rheum* 1998; **41**: 736–9.
12 Srivastava A. Dose and response in haemophilia – optimization of factor replacement therapy. *Br J Haematol* 2004; **127**: 12–25.
13 Brown DL, Hardisty RM, Kosoy MH, Bracken C. Antihaemophilic globulin: preparation by an improved cryoprecipitation method and clinical use. *Br Med J* 1967; **2**: 79–85.
14 Honig GR, Forman EN, Johnston CA, Seeler RA, Abildgaard CF, Schulman I. Administration of single doses of AHF (factor VIII) concentrates in the treatment of hemophilic hemarthroses. *Pediatrics* 1969; **43**: 26–33.
15 Britton M, Harrison J, Abildgaard CF. Early treatment of hemophilic hemarthroses with minimal dose of new factor 8 concentrate. *J Pediatr* 1974; **85**: 245–7.
16 Abildgaard CF. Current concepts in the management of hemophilia. *Semin Hematol* 1975; **12**: 223–32.
17 Ashenhurst JB, Langehannig PL, Seeler RA. Early treatment of bleeding episodes with 10 U/kg of factor VIII. *Blood* 1977; **50**: 181–2.
18 Penner JA, Kelly PE. Lower doses of factor VIII for hemophilia. *N Engl J Med* 1977; **297**: 401.
19 Weiss AE. Doses of factor VIII for hemophilic bleeding. *N Engl J Med* 1977; **297**: 1237–8.
20 Ripa T, Scaraggi FA, Ciavarella N. Early treatment of hemophilia with minimal doses of factor VIII or factor IX. *Blood* 1978; **51**: 763.
21 Allain JP. Dose requirement for replacement therapy in hemophilia A. *Thromb Haemost* 1979; **42**: 825–31.
22 Stirling ML, Prescott RJ. Minimum effective dose of intermediate factor-VIII concentrate in haemophiliacs on home therapy. *Lancet* 1979; **1**: 813–4.
23 Aronstam A, Wasssef M, Choudhury DP, Turk PM, McLellan DS. Double-blind controlled trial of three dosage regimens in treatment of haemarthroses in haemophilia A. *Lancet* 1980; **1**: 169–71.
24 Aronstam A, Wassef M, Hamad Z, Aston DL. The identification of high-risk elbow hemorrhages in adolescents with severe hemophilia A. *J Pediatr* 1981; **98**: 776–8.
25 Aronstam A, Wassef M, Hamad Z. Low doses of factor VIII for selected ankle bleeds in severe haemophilia A. *Br Med J (Clin Res Ed)* 1982; **284**: 790.
26 Bray GL, Gomperts ED, Courter S *et al.* A multicenter study of recombinant factor VIII (recombinate): safety, efficacy, and inhibitor risk in previously untreated patients with hemophilia A. The Recombinate Study Group. *Blood* 1994; **83**: 2428–35.
27 Abshire TC, Brackmann HH, Scharrer I *et al.* Sucrose formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia A in home therapy – International Kogenate-FS Study Group. *Thromb Haemost* 2000; **83**: 811–6.
28 Courter SG, Bedrosian CL. Clinical evaluation of B-domain deleted recombinant factor VIII in previously treated patients. *Semin Hematol* 2001; **38**(2 Suppl. 4): 44–51.
29 Rothschild C, Scharrer I, Brackmann HH *et al.* European data of a clinical trial with a sucrose formulated recombinant factor VIII in previously treated haemophilia A patients. *Haemophilia* 2002; **8**(Suppl. 2): 10–4.
30 World Federation of Haemophilia. *Guidelines for the Management of Haemophilia*. Quebec: WFH publication, 2009.
31 Medical Advisory Committee of Haemophilia Foundation of New Zealand. *National Guidelines – Management of Haemophilia*. Wellington: Medical Advisory Committee of Haemophilia Foundation of New Zealand, 2009.
32 Gringeri A. Treatment protocol of haemophilia and other congenital bleeding disorders in Italy. Italian Association of Hemophilia Centers (AICE). *Haemophilia* 1998; **4**: 423–4.
33 Santagostino E, Mannucci PM, Bianchi BA. Guidelines on replacement therapy for haemophilia and inherited coagulation disorders in Italy. *Haemophilia* 2000; **6**: 1–10.
34 GREHCO (Groupe de Recherche et d'Etudes de l'Hémophilie du Centre et de l'Ouest). *Le traitement de l'hémophilie*. 2e Edition. Paris: Flammarion Medecine-Science, 2002.

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35 Bundesärztekammer (German Medical Association). *Querschnitts-Leitlinien (BAK) zur Therapie mit blutkomponenten und Plasmaderivaten* (Cross-sectional Guidelines for Therapy with Blood Components and Plasma Derivatives). Deutscher Arzteverlag: Germany Bundesärztekammer, 2009: 170–8. Available in English at http://www.bundesaerztekammer.de/downloads/LeitCrossBloodComponents4ed.pdf. on 22 October 2010.
36 Berntorp E. Guidelines on treatment of haemophilia in Sweden. *Haemophilia* 1998; **4**: 425–6.
37 Mahlangu JN, Gilham A. Guideline for the treatment of haemophilia in South Africa. *S Afr Med J* 2008; **98**(2 Pt 2): 126–40.
38 Kasper CK. Protocols for the treatment of haemophilia and von Willebrand disease. *Haemophilia* 2000; **6**(Suppl. 1): 84–93.
39 Srivastava A, Chuansumrit A, Chandy M, Duraiswamy G, Karagus C. Management of haemophilia in the developing world. *Haemophilia* 1998; **4**: 474–80.
40 Elander J, Barry T. Analgesic use and pain coping among patients with haemophilia. *Haemophilia* 2003; **9**: 202–13.
41 van Veen JJ, Gleeson DC, Makris M. Paracetamol/acetaminophen usage in haemophilia: more caution needed? *Haemophilia* 2008; **14**: 434–5.
42 Rattray B, Nugent DJ, Young G. Celecoxib in the treatment of haemophilic synovitis, target joints, and pain in adults and children with haemophilia. *Haemophilia* 2006; **12**: 514–7.
43 Tsoukas C, Eyster ME, Shingo S *et al.* Evaluation of the efficacy and safety of etoricoxib in the treatment of hemophilic arthropathy. *Blood* 2006; **107**: 1785–90.
44 Rattray B, Nugent DJ, Young G. Rofecoxib as adjunctive therapy for haemophilic arthropathy. *Haemophilia* 2005; **11**: 240–4.
45 Solomon SD. Cyclooxygenase-2 inhibitors and cardiovascular risk. *Curr Opin Cardiol* 2006; **21**: 613–7.
46 Shupak R, Teitel J, Garvey MB, Freedman J. Intraarticular methylprednisolone therapy in hemophilic arthropathy. *Am J Hematol* 1988; **27**: 26–9.
47 Kisker CT, Burke C. Management of hemarthrosis. *N Engl J Med* 1970; **282**: 1212–3.
48 Kisker CT, Burke C. Double-blind studies on the use of steroids in the treatment of acute hemarthrosis in patients with hemophilia. *N Engl J Med* 1970; **282**: 639–42.
49 Magistro CM. Hyaluronidase by iontophoresis in the treatment of edema. *Phys Ther* 1964; **44**: 169–75.
50 Gandini S, Panicucci F. [Cutaneous iontophoresis of hyaluronidase in the treatment of hemorrhages in hemophilic patients]. *Electrodiagn Ther* 1977; **14**: 99–105.
51 Costello CT, Jeske AH. Iontophoresis: applications in transdermal medication delivery. *Phys Ther* 1995; **75**: 554–63.
52 Rodriguez-Merchan E. Articular bleeding (hemarthrosis) in haemophilia – an orthopedist's point of view. *The Treatment of Haemophilia (World Federation of Haemophilia Monograph)* 2008; **23**: 1–11.
53 Cazenave A, Baert D, Malet T. Post-traumatic hemarthrosis of the knee and arthroscopy. Review of 161 cases. *J Chir (Paris)* 1990; **127**: 522–7.
54 Sarimo J, Rantanen J, Heikkila J, Helttula I, Hiltunen A, Orava S. Acute traumatic hemarthrosis of the knee. Is routine arthroscopic examination necessary? A study of 320 consecutive patients. *Scand J Surg* 2002; **91**: 361–4.
55 Kerr CB. Aspiration treatment of acute haemarthroses. *Bibl Haematol* 1965; **23**: 1319–20.
56 Ingram GI, Mathews JA, Bennett AE. Controlled trial of joint aspiration in acute haemophilic haemarthrosis. *Ann Rheum Dis* 1972; **31**: 423.
57 Banta JV, Boone DC, Smith CF. Arthrocentesis of the knee in acute hemophilic arthropathy. *West J Med* 1975; **122**: 285–8.
58 Robertson JD, Connolly B, Hilliard P, Wedge J, Babyn P, Carcao M. Acute haemarthrosis of the hip joint: rapid convalescence following ultrasound-guided needle aspiration. *Haemophilia* 2009; **15**: 390–3.
59 Gregg G. The haemophiliac joint and its treatment by physical methods. *Physiotherapy* 1964; **50**: 394–8.
60 d'Young AI. Domiciliary application of CryoCuff in severe haemophilia: qualitative questionnaire and clinical audit. *Haemophilia* 2008; **14**: 823–7.
61 Wilson DJ, Lardy-Smith PD, Woodham CH, MacLarnon JC. Diagnostic ultrasound in haemophilia. *J Bone Joint Surg Br* 1987; **69**: 103–7.
62 Mauser-Bunschoten EP, Zijl JA, Mali W, van Rinsum AC, Van Den Berg HM, Roosendaal G. Successful treatment of severe bleeding in hemophilic target joints by selective angiographic embolization. *Blood* 2005; **105**: 2654–7.
63 Klamroth R, Gottstein S, Essers E, Landgraf H, Wilaschek M, Oldenburg J. Successful angiographic embolization of recurrent elbow and knee joint bleeds in seven patients with severe haemophilia. *Haemophilia* 2009; **15**: 247–52.
64 Donfield SM, Astermark J, Lail AE, Gilbert SA, Berntorp E. Value added: increasing the power to assess treatment outcome in joint haemorrhages. *Haemophilia* 2008; **14**: 276–80.

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